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The effect of smoking intensity on all-cause and cause-specific mortality – a Mendelian randomisation analysis

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Key messages:

- Observational studies indicate that even low intensity smoking increase mortality
- We used Mendelian randomisation to investigate the causal associations between smoking intensity and all-cause and cause-specific mortality
- Our study suggests that increased smoking intensity increases all-cause mortality, and mortality by respiratory disease and neoplasms
- Our study finds weaker evidence of a causal effect of smoking intensity on death by circulatory disease. This is consistent with the effect of being a smoker compared to not being a smoker being stronger than the effect of higher compared to lower smoking intensity on cardiovascular health.

Abstract

Background: Smoking is an important cause of mortality, and recent studies have suggested that even low intensity smoking might be associated with increased mortality. Still, smoking is associated with lower socioeconomic status as well as other potential risk factors, and disease onset might motivate smoking cessation, thus, residual confounding and reverse causality might bias results. We aimed to assess the evidence of a causal relationship between smoking intensity and cause-specific as well as all-cause-mortality using Mendelian randomisation analyses.

Methods: We included 56,019 participants from the Norwegian HUNT2 Study and 337,103 participants from the UK Biobank, linked to national registry data on causes of death. We estimated associations of self-reported smoking as well as the genetic variant rs1051730 as an instrument for smoking intensity with all-cause and cause-specific mortality. We subsequently meta-analysed the results from the two cohorts.

Results: Each effect allele of the rs1051730 was associated with a 9% increased hazard of all-cause mortality (95% confidence interval 6-11%) among ever smokers. Effect alleles were also associated with death by neoplasms (HR 1.11, 95% CI 1.06-1.15), circulatory diseases (HR 1.06, 95% CI 1.01-1.11), and respiratory diseases (HR 1.15, 95% CI 1.05-1.26) among ever smokers. The association was stronger among ever than never smokers for all-cause mortality ($p < 0.001$), neoplasms ($p=0.001$) and respiratory diseases ($p=0.038$).

Conclusions: Our results indicate a causal effect of smoking intensity on all-cause mortality and death by neoplasms and respiratory diseases. There was weaker evidence of a causal effect of smoking intensity on death by circulatory diseases.

Key words: genetic variation, cigarette smoking, cause of death, epidemiology

Introduction

The association between tobacco smoking and increased mortality has been recognized for several decades (1). The association with cardiovascular diseases, cancer and respiratory diseases is well established (2, 3), and suggestive evidence exists for associations with several other diseases (4). There is a clear dose-response relationship between smoking and mortality (5, 6), and risk attenuates after smoking cessation (7). Although there may be health benefits from reducing tobacco consumption from high to low intensity, the effect seems to be small (8, 9) and even long-term very low intensity smoking has recently been associated with mortality (6) and cardiovascular diseases (10).

The prevalence of heavy smoking has decreased over time in high income countries (11), while the prevalence of low intensity smoking has been more stable, thereby constituting a larger share of smokers (12). However, there is a clear social gradient in smoking (13), and smoking intensity is also higher among individuals with lower educational attainment (14). Moreover, smoking is associated with other health behaviours, and diseases onset could motivate smoking cessation. Residual confounding and reverse causality are therefore critical issues in studies of consequences of smoking.

The presumed causality between smoking and all-cause mortality has been supported by a study using Mendelian randomisation (15, 16). Two single nucleotide polymorphisms (SNPs) rs1051730 and rs16969968 are strongly associated with tobacco consumption among smokers. This association is believed to be causal for rs16969968 and the two SNPs are in perfect linkage disequilibrium with each other and considered interchangeable (17). They are located in the CHRNA5-A3-B4 nicotinic receptor gene cluster, and each additional copy of the effect allele corresponds to about one additional cigarette per day among smokers, with even stronger associations observed for objective measures of tobacco consumption (18). The rs1051730 can thus, under the assumptions that the risk alleles are evenly distributed within the population and have no effects on outcome other than

through smoking behaviour, serve as an uncounfounded measure of smoking intensity (16). As smoking intensity can only affect mortality among smokers, we would expect associations between the SNP and mortality among ever smokers only. Never smokers can therefore be used as a negative control population, and any association between the SNP and outcomes among never smokers would suggest that the SNP is not a valid instrument for smoking intensity (19). However, stratification on smoking status could also induce collider bias if the SNP is associated with smoking initiation or cessation (20).

We aimed to expand the existing literature by assessing the evidence of a causal relationship between smoking intensity and cause-specific as well as all-cause-mortality, using Mendelian randomisation (16).

Methods

Study design

We performed Mendelian randomisation analyses of the associations between the single nucleotide polymorphism rs1051730 and all-cause and cause-specific mortality in two different study cohorts; the second wave of the Nord-Trøndelag Health Study (the HUNT2 Study 1995-97) and the UK Biobank (2006-2010). We subsequently meta-analysed the effect estimates. For comparison, we also estimated the association between self-reported smoking and mortality. Further details about the study populations and genotyping can be found in the web appendix.

Smoking behaviour

For analyses of self-reported smoking status, we categorised participants as never smokers, former smokers, current low intensity smokers (<10 cigarettes per day), medium intensity smokers (10-19 cigarettes per day) or high intensity smokers (20 or more cigarettes per day). For the main Mendelian randomisation analyses, we combined former and current smokers into ever smokers, in order to

avoid potential collider bias. However, assuming that the effects of smoking intensity on mortality are reversible, we would expect stronger association among current compared to former smokers. We therefore additionally categorized smokers in five subgroups based on time since smoking cessation: current smokers, former smokers who quit less than 5 years, 5-9 years, 10-19 years or ≥ 20 years before baseline, respectively.

Outcome

Date and cause of death until December 31st 2012 were collected from the Cause of Death Registry in Norway and until June 2017 in the UK. We defined all-cause mortality as death from any cause. To identify specific causes of death, we first recoded cause of death from ICD-9 to ICD 10 (21) for a total of 13 HUNT2-participants who died before 1996. Second, we categorised causes of death according to the European short list of causes of death (see Supplementary Table S1) (22).

We excluded diseases of blood, blood-forming organs and immune system, skin and subcutaneous tissue, complications of pregnancies, conditions originating in the perinatal period and congenital malformations and chromosomal abnormalities (ICD-10 codes D50-D89, O00-Q99) from the analyses of cause-specific mortality, due to few deaths from these causes.

Statistical analyses

We assessed the statistical evidence of an association between number of effect alleles and possible confounders within strata of smoking status, using linear regression for continuous variables and chi square test for categorical variables.

All associations were analysed separately within the UK Biobank and the HUNT2 cohorts, and estimates from the two cohorts were subsequently meta-analysed. A random effects model was used for associations with self-reported smoking, whereas associations with the genetic instrument were performed assuming a fixed effect. We additionally performed random effects meta-analyses

because I^2 indicated substantial heterogeneity for several causes of death. We performed analyses using complete cases in Stata 15.0 and R (R Core Team, 2014).

Associations with self-reported smoking

We analysed the association between self-reported smoking status and mortality using Cox proportional hazard models with age as the time scale, adjusted for alcohol intake and in strata of education and sex. The association between smoking and body mass index is likely bidirectional; as smoking is associated with lower body mass index, a high body mass index can motivate smoking initiation (23, 24). We considered the mediating effect to be more important than the confounding effect in a setting with mostly middle-aged study participants, and hence did not adjust for body mass index. Different causes of mortality were assessed in separate models, and participants were censored at time of death from any other cause than the one used as an outcome in any given model, as well as at time of emigration or end of follow-up. We assessed the proportional hazards assumption using Schoenfeld residuals and visual inspection of log-log plots. Due to indication of non-proportionality, we performed additional analyses in strata of age.

Mendelian randomisation

We similarly analysed the association between the rs1051730 effect allele and death using Cox proportional hazards models with age as the time scale, and stratified by sex. As the association between the SNP and number of cigarettes smoked was consistent with an additive effect, we treated number of effect alleles as a continuous variable in the analyses.

As smoking intensity can only affect mortality among smokers, we would expect associations between the SNP and mortality among ever smokers only. We therefore performed analyses separately for ever smokers and never smokers, and we report the statistical evidence of heterogeneity in the association over these subgroups as the p for difference.

Shoenfeld's residuals did not provide statistical evidence of non-proportional hazards for the association between the SNP and mortality in strata of smokers/never smokers. We still examined the association separately before and after age 80 as visual inspection of log-log plots indicated possible violation of the proportional hazards assumptions. These analyses were performed in the HUNT Study only, as there were no deaths after age 80 in the UK Biobank sample.

To assess the potential benefit of smoking cessation, we also performed Mendelian randomisation analyses separately for five groups based on current smoking status and time since smoking cessation for former smokers.

Results

Our study sample included 56,019 participants from the HUNT2 Study and 337,103 participants from the UK Biobank. Of these, 11,303 and 9634 participants, respectively, died within follow-up. The most common causes of death were neoplasms and diseases of the circulatory system (Supplementary Table S1). Participants in the HUNT2 Study were followed for up to 17.4 years , and median age at death was 82 years (interquartile range 75-88) compared to a maximum of 11 years of follow-up and a median age at death of 67 years (interquartile range 62-70) in the UK Biobank sample.

We confirmed the association between rs1051730 and intensity of smoking; for each effect allele, current smokers smoked on average 0.7 cigarettes (95% confidence interval (CI) 0.5-0.8) more per day in the HUNT2 Study and 1.0 (95% CI 0.9 to 1.1) cigarettes more per day in the UK Biobank sample, with a near linear increase in number of cigarettes smoked per effect allele alleles. The SNP was also associated with being a current rather than former smoker ($p<0.001$) and with lower age at participation among ever smokers ($p=0.005$ in the HUNT Study, $p=0.002$ in the UK Biobank). Possible confounders were evenly distributed according to number of effect alleles (Supplementary Tables S2

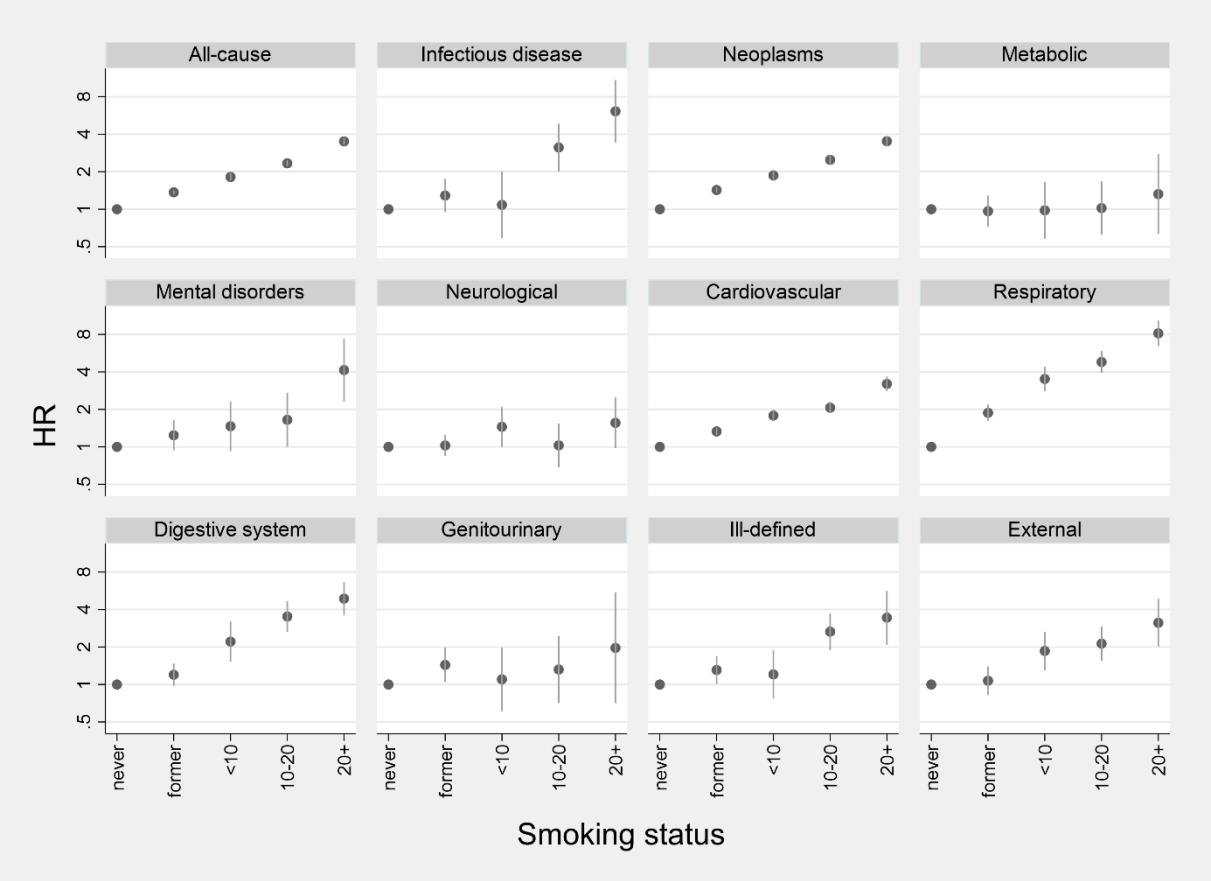
to S5). For each risk allele, the odds of ever having smoked daily increased with 2% (95% CI 1-3%, p<0.001) and 4% (95% CI 1-6%, p=0.005) in the UK Biobank Study and the HUNT Study, respectively.

Self-reported smoking

We found a clear dose-response relationship between self-reported smoking and all-cause mortality, mortality by neoplasm, circulatory and respiratory diseases, diseases of the digestive system and external causes of death (Figure 1). Former smokers had an intermediate risk between never and low intensity smokers for all of these causes of death, except that there was no increased risk of death by external causes for former compared to never smokers. We found indication of non-proportionality of hazards for all-cause mortality and death by mental disorders, neurological, circulatory, and respiratory diseases. Additional analyses indicated weaker associations between smoking and mortality at older ages (Supplementary Tables S8 and S9).

Figure 1: Associations between smoking status (given as never smoker, former smoker or by number of cigarettes smoked per day among current smokers) and mortality, results from a random effects meta-analysis of estimates from the HUNT2 Study (1995-97) (n=52,561) and the UK Biobank (2006-

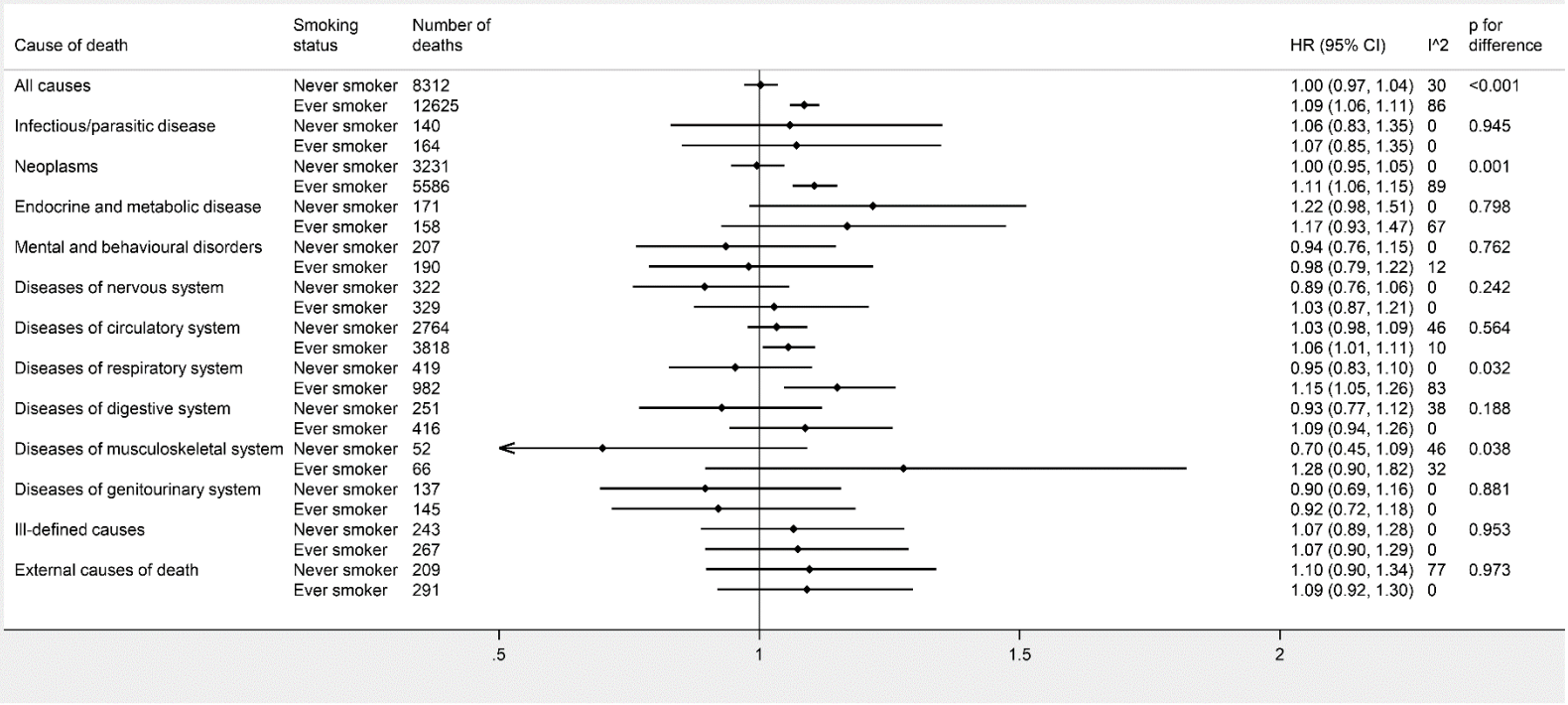
2010). Graphs are truncated at hazard ratio=0.5



Mendelian randomisation analyses

Mendelian randomisation analyses indicated a causal mechanism behind the observed association between smoking intensity and all-cause mortality among ever smokers (hazard ratio (HR) 1.09, 95% CI 1.06 to 1.11 per risk allele – see Figure 2). Furthermore, Mendelian randomisation results supported a causal effect of smoking intensity on death by neoplasms (HR 1.11, 95% CI 1.06 to 1.15 per risk allele) and respiratory diseases (HR 1.15, 95% CI 1.05 to 1.26 per risk allele). Number of effect alleles was not associated with higher mortality from either of these causes among never smokers (HRs 1.00, 1.00 and 0.95, and p for difference <0.001, 0.001 and 0.032, respectively).

Figure 2: Associations between number of smoking increasing alleles of rs1071530 and mortality, results from a fixed effect meta-analysis of estimates from the HUNT2 Study (1995-1997) and UK Biobank (2006-2010).



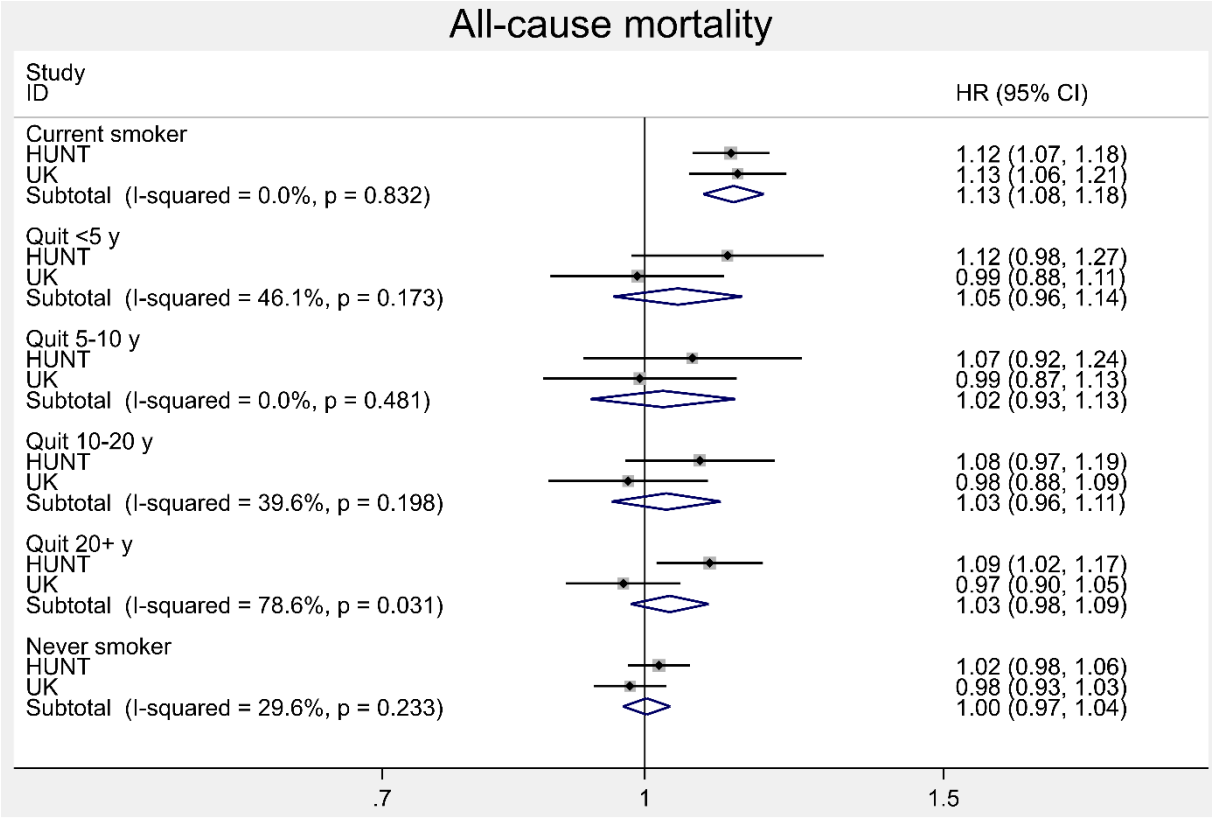
Each effect allele was associated with 6% (95% CI 1 to 11%) increased hazard rate of death by circulatory diseases among ever smokers. The effect estimate among never smokers was only marginally smaller (HR 1.03, 95% CI 0.98-1.09), with weak statistical evidence of a difference (p for difference 0.568). In additional analyses, this association among never smokers was only found among those 80 years or older in the HUNT2 Study (Supplementary Table S12 and Supplementary Figure S8). Furthermore, we found some statistical evidence that the association between effect alleles and mortality by musculoskeletal diseases differed between smokers and non-smokers (p for difference 0.038), but there was only weak evidence of an association among ever smokers (HR 1.28, 95% CI 0.90 to 1.82) and we did not find a corresponding association with self-reported smoking intensity.

For all other causes of death, we did not find strong statistical evidence of either associations between effect alleles and mortality among ever smokers or a stronger association among ever compared to never smokers.

There was substantial heterogeneity between the estimates from the HUNT2 Study and the UK Biobank for several outcomes (I^2 up to 89%). Random effects meta-analyses gave similar effect estimates as fixed effect meta-analyses, but with lower precision (Supplementary Figure S2).

Furthermore, we found low heterogeneity between the HUNT2 Study and the UK Biobank in the association among current smokers, whereas there was substantial heterogeneity among former smokers (Figure 3 and Supplementary Figures S3-S14), and analyses of current smokers supported a causal effect of smoking intensity on all-cause mortality and death by neoplasm and respiratory diseases. We found only weak statistical evidence of an association between effect alleles and death by circulatory disease among current smokers (HR 1.05, 95% CI 0.97-1.13, p=0.213), but with low heterogeneity between the HUNT2 Study and the UK Biobank. For all-cause mortality and death by neoplasms, meta-analyses indicated that the excess risk associated with each effect allele attenuated with time, whereas the results were not clear-cut for the other causes of death (Figure 3 and Supplementary Figures S3-S14). The association between effect alleles and death by circulatory diseases did not seem to attenuate with time since smoking cessation.

Figure 3: Associations between number of smoking increasing alleles of rs1071530 and all-cause mortality, results from a fixed effect meta-analysis of estimates from the HUNT2 Study (1995-1997) (n=55.593) and UK Biobank (2006-2010). Results are presented separately by smoking status.



Discussion

Using data from two large-scale cohort studies, we observed a clear dose-response relationship of self-reported smoking with all-cause mortality and mortality by neoplasm, circulatory diseases, respiratory diseases, diseases of the digestive system, and external causes of death. Mendelian randomisation analyses indicated a causal mechanism behind the observed association for all-cause mortality as well as for death by neoplasms and respiratory diseases. We found weaker evidence for a causal effect of smoking intensity on circulatory diseases as well.

Strengths and limitations

The validity of Mendelian randomisation analyses relies on three main assumptions: 1) the genetic instrument must be associated with the exposure of interest, 2) it must only be associated with the outcome through the exposure of interest, and 3) it must be independent of confounders. The association between rs157030 and smoking intensity has been established previously, and was confirmed in our study samples. The second and third assumptions cannot be directly verified, but can be supported by lack of associations between effect alleles and known confounders and by use of negative controls (19). An association between effect alleles and age at participation among ever smokers is to be expected, as smoking intensity increases mortality. The lack of associations between effect alleles and mortality among never smokers support the interpretation of a causal effect of smoking intensity on all-cause mortality, as well as death by neoplasms and respiratory diseases. A full instrumental variable estimation of the causal effect per cigarette smoked was not possible as the number of cigarettes smoked does not fully describe the effect of the SNP on tobacco consumption (18).

In the Mendelian randomisation analyses, we adjusted for age and sex only, both of which had complete data, and missing on smoking status was a negligible problem. However, there is the potential for misclassification of the self-reported smoking variables. Misclassification of ever smokers as never smokers would bias the use of never smokers as a negative control; however, we have no indication of this from the analyses of all-cause mortality. Dates and causes of deaths were collected from national registries, we thus had the best information available about causes of death; however, as causes of death are rarely determined based on post-mortem examinations, we cannot exclude misclassifications in causes of death either. This study gives a broad overview of the associations between a genetic variant associated with smoking intensity and mortality, but combining causes into broad categories could also mask the association with specific sub-causes.

Furthermore, whereas genetic variants are determined at conception, study participants did not enter the studies until adulthood. As we lack information about the association between effect alleles and mortality before study inclusion, there is a possibility that lower survival among exposed individuals could bias the results (25).

Participation in the HUNT2 Study was about 70% (26), and the HUNT2 Study is fairly representative of the general population, but despite this, non-participants in the HUNT2 Study tend to have somewhat higher mortality as compared to participants (27). In contrast, participation in the UK Biobank was only about 5%, suggesting a higher selection to participation (28). Representative samples are not a prerequisite for valid associations in longitudinal studies (29). Still, selective participation could induce bias (30). While the low mortality associated with effect alleles among former smokers in the UK Biobank sample could be due to selection bias, the consistency of estimated associations between the two samples among current smokers suggest that selection bias is a lesser problem for this group of participants.

We found a weak association of the SNP with smoking initiation and stronger evidence of an association with smoking cessation. However, we found only weak evidence of associations between the SNP and important confounders within strata of smoking status. This weighs against any important collider bias being introduced by stratification, but we still cannot exclude it (17).

Comparison with other studies

Evidence of a causal effect of smoking intensity on all-cause mortality, deaths by neoplasms and respiratory diseases is consistent with existing knowledge about the consequences of smoking (3). A possible effect of smoking intensity on death by musculoskeletal and connective tissue diseases should not be given much emphasis, as the estimates were imprecise and inconsistent between methods. On the other hand, smoking has previously been associated with rheumatoid arthritis and systemic lupus erythematosus (3).

Although smoking is also a well-established risk factor for circulatory diseases, our findings regarding a causal link were not conclusive. As effect estimates were similar among never compared to ever smokers, we cannot exclude pleiotropic effects of the SNP as an explanation. However, the finding of an association between the effect allele and death from circulatory diseases among never smokers was inconsistent, and the modest association found in ever smokers might therefore still represent a causal effect of smoking intensity on death by circulatory diseases. The gradient in risk associated with self-reported smoking intensity is also gentler for death by circulatory diseases, compared to neoplasms and respiratory diseases. This is in accordance with a recent review, in which smoking just one cigarette per day was found to confer up to half of the excess relative risk of cardiovascular diseases associated with smoking 20 cigarettes per day (10). Finding evidence of a weak causal effect only is thus consistent with the effects of smoking on circulatory diseases depending more on smoking status than on smoking intensity.

Our results did not indicate causality in the associations of smoking with infectious diseases, diseases of the digestive system, and renal failure previously identified by Carter et al (4), although, again, it is important to bear in mind that the SNP we used is mainly an instrument of smoking intensity, not smoking status.

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Ethical approval

All participants in the HUNT2 Study and the UK Biobank gave their informed consent to participation. The present study was approved by the Regional Ethical Committee in Mid-Norway (REK-2011/975) and the UK Biobank has received ethics approval from the National Health Service National Research Ethics Service (ref 11/NW/0382).

Conflict of interest

The authours declare no conflicts of interest

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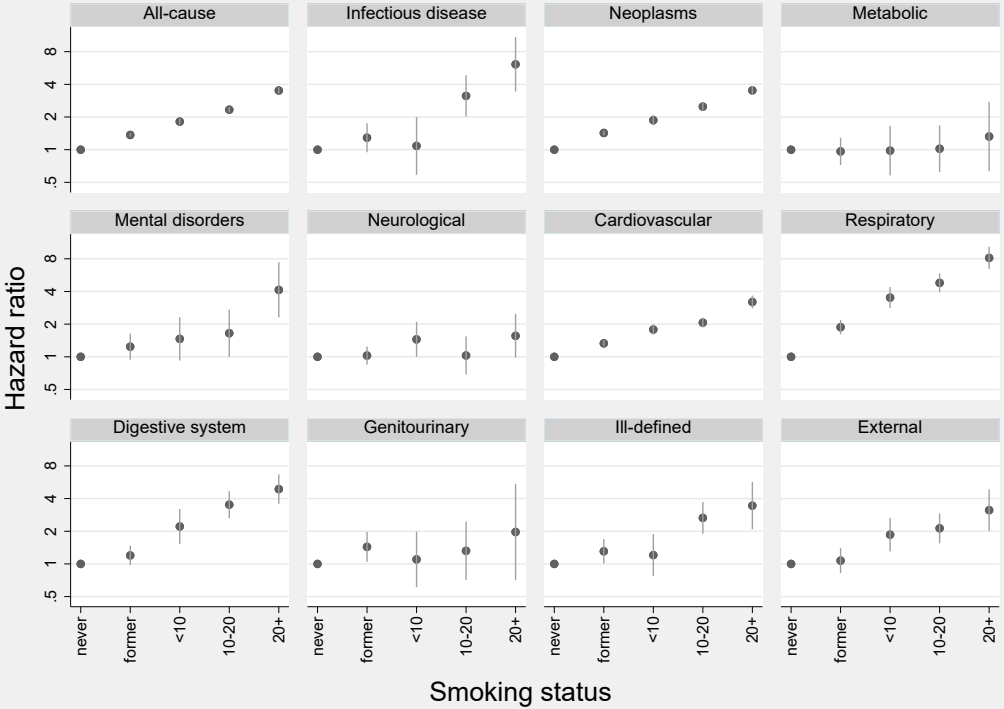
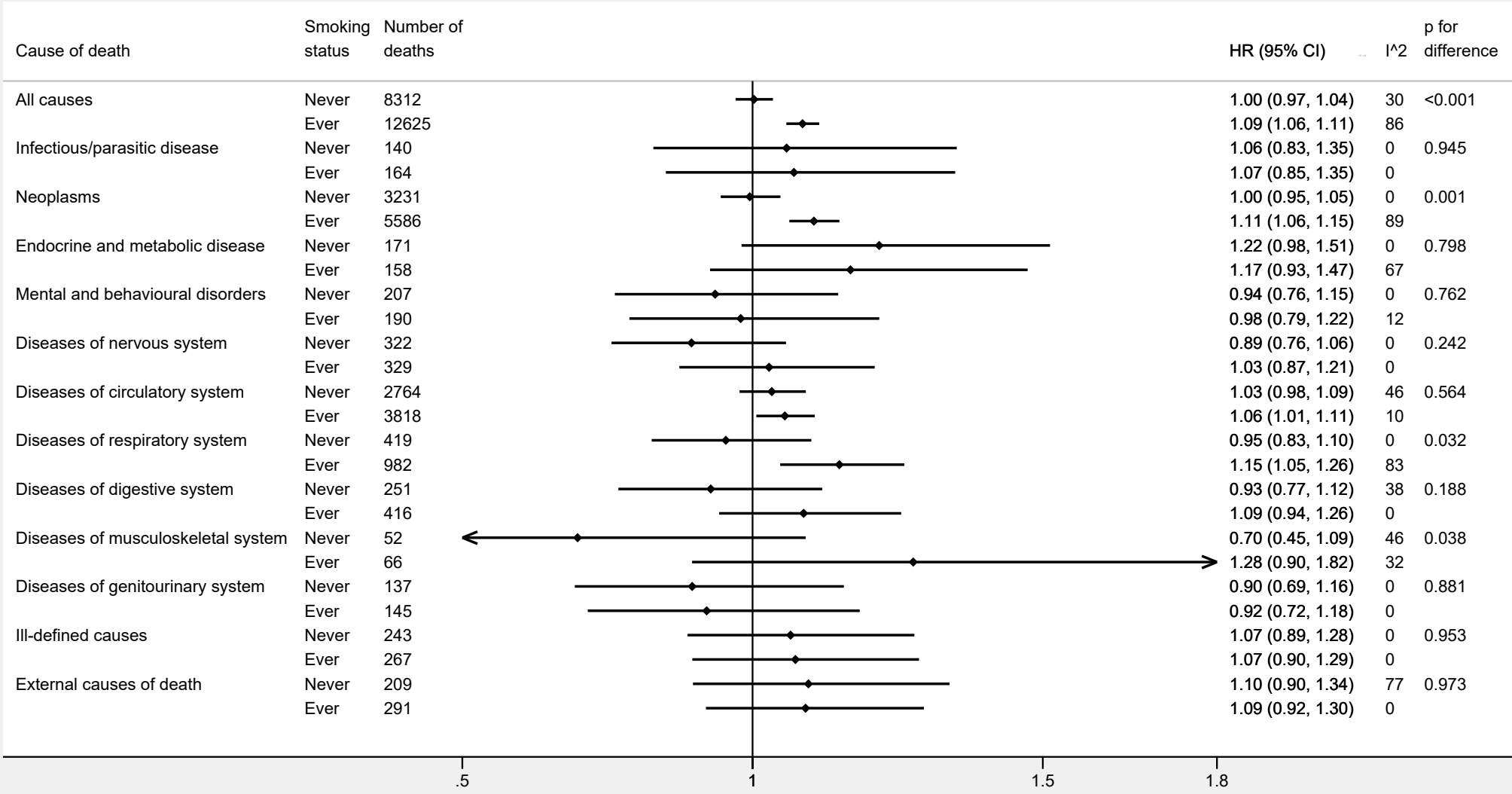
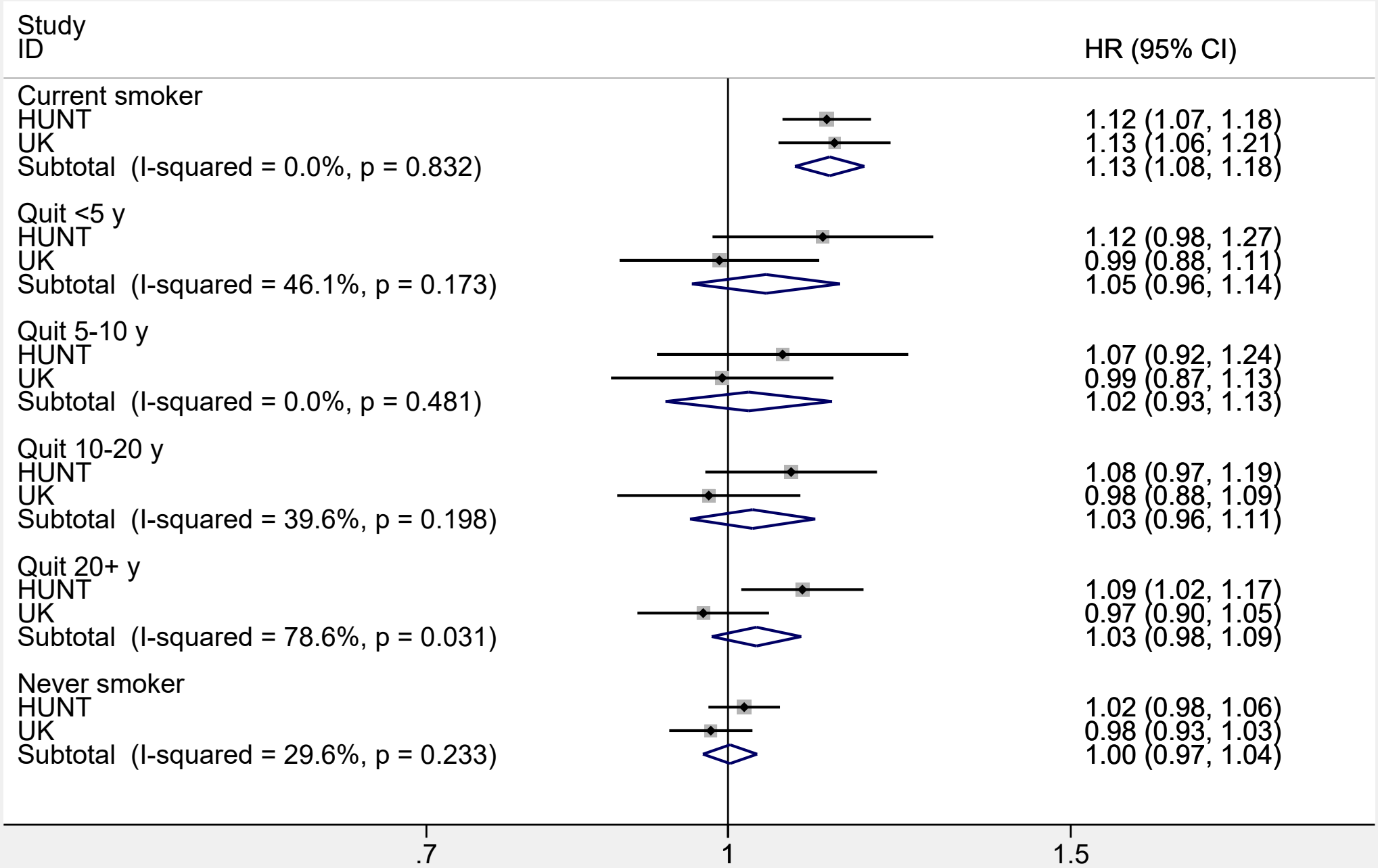

All-cause
Infectious disease
Neoplasms
Metabolic
Mental disorders
Neurological
Cardiovascular
Respiratory
Digestive system
Genitourinary
Ill-defined
External
Hazard ratio
.5
1
2
4
8
never
former
<10
10-20
20+
Smoking status


Cause of death
Smoking status
Number of deaths
HR (95% CI)
I^2
p for difference
All causes Never 8312 1.00 (0.97, 1.04) 30 <0.001
Ever 12625 1.09 (1.06, 1.11) 86
Infectious/parasitic disease Never 140 1.06 (0.83, 1.35) 0 0.945
Ever 164 1.07 (0.85, 1.35) 0
Neoplasms Never 3231 1.00 (0.95, 1.05) 0 0.001
Ever 5586 1.11 (1.06, 1.15) 89
Endocrine and metabolic disease Never 171 1.22 (0.98, 1.51) 0 0.798
Ever 158 1.17 (0.93, 1.47) 67
Mental and behavioural disorders Never 207 0.94 (0.76, 1.15) 0 0.762
Ever 190 0.98 (0.79, 1.22) 12
Diseases of nervous system Never 322 0.89 (0.76, 1.06) 0 0.242
Ever 329 1.03 (0.87, 1.21) 0
Diseases of circulatory system Never 2764 1.03 (0.98, 1.09) 46 0.564
Ever 3818 1.06 (1.01, 1.11) 10
Diseases of respiratory system Never 419 0.95 (0.83, 1.10) 0 0.032
Ever 982 1.15 (1.05, 1.26) 83
Diseases of digestive system Never 251 0.93 (0.77, 1.12) 38 0.188
Ever 416 1.09 (0.94, 1.26) 0
Diseases of musculoskeletal system Never 52 0.70 (0.45, 1.09) 46 0.038
Ever 66 1.28 (0.90, 1.82) 32
Diseases of genitourinary system Never 137 0.90 (0.69, 1.16) 0 0.881
Ever 145 0.92 (0.72, 1.18) 0
Ill-defined causes Never 243 1.07 (0.89, 1.28) 0 0.953
Ever 267 1.07 (0.90, 1.29) 0
External causes of death Never 209 1.10 (0.90, 1.34) 77 0.973
Ever 291 1.09 (0.92, 1.30) 0
.5
1
1.5
1.8

All-cause mortality



Supplementary data to
The effect of smoking intensity on all-cause and cause-specific mortality – a Mendelian randomisation analysis

Supplementary methods

Study populations

The HUNT Study

The HUNT Study is a large total population-based health study in which all inhabitants of Nord-Trøndelag County aged 20 years or older have been invited to participate. In the second wave of the study (the HUNT2 Study, 1995-97), 69.5% of the invited participated (n=65,237) (1). Questionnaires covered a range of topics regarding health, diseases, behavioural risk factors and social and socioeconomic conditions, anthropometric data was measured and non-fasting venous blood samples were drawn (1). The study sample consisted of 56,019 individuals with genotype data (Supplementary Figure S1).

The UK Biobank

The UK Biobank is a national health resource, which recruited individuals at assessment centres located across the UK from 2006 to 2010 (2). In total, data was collected on 502,647 participants aged between 40 and 69 years. Collected measures cover a wide range of physical, cognitive and mental health outcomes as well as many risk factors including smoking behaviour. After restricting individuals to white British ancestry, removing related individuals and applying standard genotype exclusions, 337,103 individuals were available for the current analysis. Further details of standard exclusion criteria are presented elsewhere (3).

Genetic information

The rs1051730 SNP was genotyped in DNA extracted from blood samples collected at HUNT2, using a TaqMan assay (Assay ID: C_9510307_20, Applied Biosystems, USA) on an Applied Biosystems 7900HT Fast Real-Time PCR System, as described earlier (4). The genotyping success rate was 99.3% (call rate cut-off 90%) and the genotype frequencies were in agreement with HapMap-CEU data (MAF = 0.335 and 0.389, respectively) (4).

In the UK Biobank, blood samples were collected at the initial assessment centre. For 49,979 participants, genotyping was conducted using the Affymetrix UK BiLEVE Axiom array and for the remaining 438,398 participants, the Affymetrix UK Biobank Axiom® array was used. Imputation and initial quality control steps were performed by the Wellcome Trust Centre for Human Genetics (5).(3). The rs1051730 SNP call rate was 100% and MAF = 0.328.

Study variables

How smoking was assessed

In each study cohort, smoking status at baseline was reported as never smoker, former smoker or current smoker of cigarettes, cigars or pipe. We excluded those who reported cigar or pipe smoke only. Current and former smokers were asked about the average number of cigarettes consumed per day, and former smokers reported the number of years since smoking cessation. Participants in the UK Biobank were asked to report 1 cigarette per gram of hand-rolled tobacco or 30 cigarettes per ounce.

Covariates in observational analyses

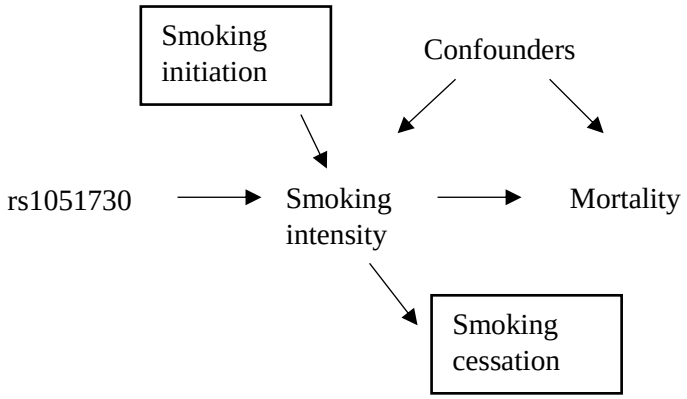
We categorized level of education at baseline as primary, secondary and tertiary education based on data from national registries in HUNT2 and self-reported in the UK Biobank. Participants in HUNT2 were asked if they were teetotallers, and about frequency of alcohol

intake per month. Participants in the UK Biobank reported frequency of alcohol intake according to the following categories: never, on special occasions, 1-3 times a month, once/twice a week, three-four times a week or daily/almost daily. We categorized frequency of alcohol intake as never, on special occasions (including those who did not state to be a teetotaller, but still reported 0 occasions per month), monthly (1-3 times a month), weekly (including once a week to four times a week or 4-15 times a month) or daily/almost daily (including 16 or more times a month).

Statistical analyses

Conditioning on smoking status and collider bias

A mutation in rs1051730 has been found to be associated with smoking intensity. This association is likely mediated through modifications of nicotinic acetylcholine receptors (6). Initiation of smoking can be considered a prerequisite for rs1051730 to increase smoking intensity; in a society fee from tobacco consumption, rs1051730 could not affect smoking intensity. Smoking cessation could, on the other hand, be considered a consequence of smoking intensity; high intensity smokers tend to be less inclined to cease smoking (7). This situation is illustrated in Supplementary Figure S1. According to this DAG, smoking initiation is not a consequence of smoking intensity and conditioning on smoking intensity should therefore not create any collider bias. Smoking cessation is, on the other hand, downstream of smoking intensity, and conditioning on smoking cessation could therefore create a collider bias.



Despite the argument that rs1051730 can only affect smoking intensity in the presence of tobacco consumption, we found indication of an association between the SNP and the likelihood of smoking initiation (OR 1.04, 95% CI 1.01-1.06 in the HUNT2 Study). Those who report to never have smoked daily might include individuals who tried smoking, but never took up smoking at a daily basis. Assuming that a substantial part of both study populations had ever tried smoking, it is therefore possible that the presence of the effect allele affected the likelihood to take up daily smoking, i.e. to initiate smoking. Reporting to be a never smoker could thus be a consequence of the effect allele, downstream to the very lowest levels of smoking intensity. Yet, the association between rs1051730 was weak, as ever smoking is frequent in the study samples (55% ever smokers in HUNT2), an OR of 1.04

corresponds to a mere one percentage point difference in frequency of ever smoking per effect allele. Given a weak to moderate association between the risk factor and the collider, conditioning on a collider will usually be a minor source of bias in Mendelian Randomisation studies (8).

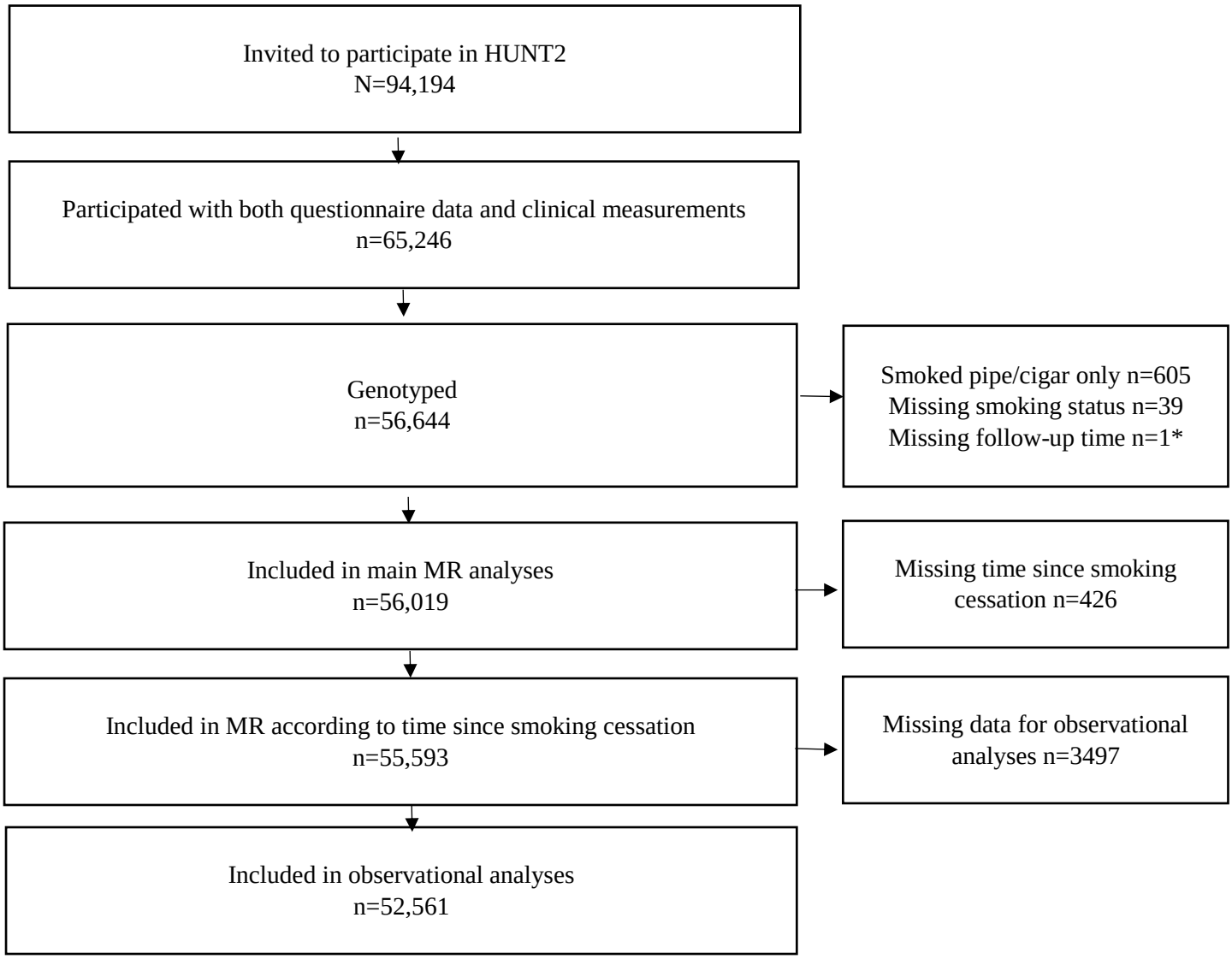
If conditioning on smoking status introduced a collider bias, we would expect to find evidence of an association between rs1051730 and measured confounders in strata of smokers. Results of these analyses are presented in Supplementary Tables S2-S5. We found weak statistical evidence that number of effect alleles were associated with education and alcohol intake

It is therefore unlikely that a collider bias introduced by conditioning on smoking initiation would introduce an important bias. The bias from conditioning on smoking cessation would likely be larger, as the association between the SNP and smoking cessation is greater (…). Considering the lack of association between the SNP and potential confounders in groups of ever/never smokers and former/current smokers, we consider it unlikely that our results are severely biased by conditioning on smoking status.

Supplementary Table S1: Coding of causes of death, and number of deaths per cause in the HUNT2 Study (1995-97, n=56,019) and the UK Biobank (2006-10, n=337,103)

EU shortlist code	Cause of death	ICD-10 codes	Number of deaths in the HUNT Study	Number of deaths in the UK Biobank
1.	Infectious and parasitic diseases	A00-B99	221	83
2.	Neoplasms	C00-D48	3138	5679
3.	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	D50-D89	32	22
4.	Endocrine, nutritional and metabolic diseases	E00-E89	258	71
5.	Mental and behavioural disorders	F01-F99	319	78
6.	Diseases of the nervous system and the sense organs	G00-H95	339	312
7.	Diseases of the circulatory system	I00-I99	4603	1979
8.	Diseases of the respiratory system	J00-J99	866	535
9.	Diseases of the digestive system	K00-K92	284	383
10.	Diseases of the skin and subcutaneous tissue	L00-L99	13	8
11.	Diseases of the musculoskeletal system/connective tissue	M00-M99	65	53
12.	Diseases of the genitourinary system	N00-N99	240	42
13.	Complications of pregnancy, childbirth and puerperium	O00-O99	0	0
14.	Certain conditions originating in the perinatal period	P00-P96	0	0
15.	Congenital malformations and chromosomal abnormalities	Q00-Q99	9	13
16.	Symptoms, signs, ill-defined causes	R00-R99	458	51
17.	External causes of morbidity and mortality	V01-Y89	457	43
	Missing cause of death in registry		1	
	Total		11 303	9634

Supplementary Figure S1: Flow-chart showing how the study sample was derived and the number of participants included in the different analyses – The HUNT2 Study (1995-97)



* This participant was missing date of participation and was therefore assigned the median date of participation as a start of follow-up. However, the participant died before the median participation date, and therefore did not contribute with follow-up time in analyses.

Supplementary Table S2: Baseline characteristics of 56,019 participants in the HUNT2 Study according to smoking status and number of rs1051730 effect alleles

	Never smokers				Ever smokers			
	0	1	2	p-value	0	1	2	p-value
Study sample (n)	11,138	10,866	2,743		13,712	13,958	3602	
Cigarettes per day (mean)					11.1	11.7	12.2	<0.001
Missing (n)					1133	1147	277	
Smoking status (%)[a]								
Current					52	55	58	
Former					48	45	43	<0.001
Men (%)	41	41	41	0.866	53	52	51	0.118
Age (mean)	49.2	49.3	49.1	0.980	50.5	50.1	49.7	0.005
Education (%)								
Primary	33	33	32		39	40	40	
Secondary	41	41	42		46	46	45	
Tertiary	26	26	26	0.723	15	15	15	0.478
Missing (n)	560	586	151		603	630	155	
Alcohol intake (%)								
Never	20	19	19		7	7	7	
Special occasions	28	29	30		26	27	27	
Monthly	35	34	35		39	39	40	
Weekly	17	17	16		28	27	26	
Daily/almost daily	0	0	0	0.331	1	1	1	0.558
Missing (n)	510	537	138		732	784	207	

[a] Smoking status was missing for 39 individuals

Supplementary Table S3: Baseline characteristics of 31,272 ever smokers in the HUNT2 Study according to current smoking status and number of rs1051730 effect alleles

	Former smokers				Current smokers			
	0	1	2	p-value	0	1	2	p-value
Study sample (n)	6536	6284	1529		7176	7674	2073	
Cigarettes per day (mean)	11.5	12.0	12.3	<0.001	10.7	11.4	12.1	<0.001
Missing (n)	891	887	212		242	260	65	
Men (%)	60	60	58	0.117	46	45	46	0.733
Age (mean)	54.3	54.0	53.9	0.275	47.0	47.0	46.5	0.370
Education (%)								
Primary	39	39	41		39	40	39	
Secondary	43	42	40		48	48	48	
Tertiary	18	18	19	0.263	13	12	13	0.260
Missing (n)	304	324	67		299	306	88	
Alcohol intake (%)								
Never	8	7	8		6	6	6	
Special occasions	28	29	28		24	25	26	
Monthly	36	36	38		42	41	41	
Weekly	28	27	25		28	27	27	
Daily/almost daily	1	1	1	0.356	1	1	1	0.634
Missing (n)	329	324	90		403	460	117	

Supplementary Table S4: Baseline characteristics of 335,918 participants in the UK Biobank according to smoking status and number of rs1051730 effect alleles

	Never smokers				Ever smokers			
	0	1	2	p-value	0	1	2	p-value
Study sample (n)	82,141	81,599	20,338		68,569	66,962	16,309	
Cigarettes per day (mean)					14.88	15.90	16.72	<0.001
Missing (n)					3807	3371	739	
Smoking status (%)[a]								
Current					22	22	22	
Former					78	78	78	0.055
Men (%)	42	41	41	0.121	52	52	52	0.549
Age (mean)	56.1	56.2	56.2	0.092	57.8	57.7	57.6	0.002
Education (%)								
Primary	14	14	14		21	21	20	
Secondary	51	50	50		51	52	52	
Tertiary	36	36	36	0.768	27	27	28	0.021
Missing (n)	683	704	202		634	685	133	
Alcohol intake (%)								
Never	7	7	7		5	6	6	
Special occasions	11	12	11		9	9	9	
Monthly	12	13	12		9	10	10	
Weekly	53	52	53		49	48	48	
Daily/almost daily	16	16	16	0.150	28	28	28	0.074
Missing (n)	33	47	16		47	55	13	

[a] Smoking status was missing for 1185 individuals

Supplementary Table S5: Baseline characteristics of 151,840 ever smokers in the UK Biobank Study according to current smoking status and number of rs1051730 effect alleles

	Former smokers				Current smokers			
	0	1	2	p-value	0	1	2	p-value
Study sample (n)	53,662	52,137	12,679		14,907	14,825	3,630	
Cigarettes per day (mean)	18.5	19.5	20.4	<0.001	14.9	15.9	16.7	<0.001
Missing (n)	20,694	18,814	4,255		3,807	3,371	739	
Men (%)	51	52	51	0.514	54	54	54	0.912
Age (mean)	58.5	58.4	58.4	0.033	55.1	55.1	54.8	0.066
Education (%)								
Primary	20	20	19		25	25	24	
Secondary	51	51	51		53	54	55	
Tertiary	29	29	30	0.033	22	22	22	0.541
Missing (n)	478	506	93		156	179	40	
Alcohol intake (%)								
Never	5	5	5		7	8	7	
Special occasions	8	9	8		12	12	14	
Monthly	8	9	9		11	11	12	
Weekly	50	49	49		43	42	41	
Daily/almost daily	28	28	29	0.286	27	27	27	0.003
Missing (n)	27	27	7		20	28	6	

Supplementary Table S6: Associations between self-reported smoking status and all-cause and cause-specific mortality in the HUNT2 Study (1995-97). N=52,561.

Cause[1]	Smoking	Deaths	HR	95 % CI		
All-cause mortality	Never smoker	4233	Ref			
	Former smoker	3181	1.28	1.21	-	1.35
	<10 cig per day	1025	1.74	1.62	-	1.87
	10-19 cig per day	1196	2.11	1.96	-	2.26
	20+ cig/day	330	2.98	2.65	-	3.36
Infectious diseases	Never smoker	101	Ref			
	Former smoker	64	1.36	0.93	-	1.99
	<10 cig per day	11	1.06	0.56	-	2.02
	10-19 cig per day	20	2.57	1.52	-	4.36
	20+ cig/day	4	3.20	1.13	-	9.10
Neoplasms	Never smoker	936	Ref			
	Former smoker	944	1.37	1.24	-	1.52
	<10 cig per day	320	1.81	1.58	-	2.06
	10-19 cig per day	471	2.40	2.13	-	2.71
	20+ cig/day	125	3.20	2.63	-	3.90
Metabolic diseases	Never smoker	124	Ref			
	Former smoker	65	0.88	0.62	-	1.24
	<10 cig per day	17	0.98	0.58	-	1.66
	10-19 cig per day	17	0.99	0.57	-	1.70
	20+ cig/day	5	1.47	0.58	-	3.73
Mental disorders	Never smoker	157	Ref			
	Former smoker	80	1.29	0.93	-	1.79
	<10 cig per day	20	1.35	0.83	-	2.19
	10-19 cig per day	19	1.76	1.05	-	2.95
	20+ cig/day	6	3.12	1.32	-	7.38
Nervous system	Never smoker	141	Ref			
	Former smoker	94	1.19	0.88	-	1.61
	<10 cig per day	29	1.42	0.93	-	2.15
	10-19 cig per day	26	1.19	0.76	-	1.88
	20+ cig/day	7	1.49	0.67	-	3.30
Circulatory diseases	Never smoker	1874	Ref			
	Former smoker	1298	1.21	1.11	-	1.31
	<10 cig per day	402	1.66	1.49	-	1.87
	10-19 cig per day	363	1.71	1.52	-	1.94
	20+ cig/day	99	2.46	1.99	-	3.04
Respiratory diseases	Never smoker	256	Ref			
	Former smoker	240	1.69	1.37	-	2.08
	<10 cig per day	110	3.50	2.75	-	4.46
	10-19 cig per day	106	4.28	3.32	-	5.51

	20+ cig/day	40	9.66	6.71	-	13.91
Digestive system	Never smoker	104	Ref			
	Former smoker	67	1.35	0.94	-	1.92
	<10 cig per day	29	2.24	1.45	-	3.46
	10-19 cig per day	43	3.87	2.58	-	5.81
	20+ cig/day	5	2.59	1.02	-	6.58
Musculoskeltal/	Never smoker	111	Ref			
connective tissue	Former smoker	75	0.72	0.36	-	1.46
	<10 cig per day	12	0.89	0.33	-	2.38
	10-19 cig per day	10	1.33	0.54	-	3.26
	20+ cig/day	3	1.14	0.15	-	8.80
Genitourinary	Never smoker	6	Ref			
	Former smoker	2	1.37	0.96	-	1.96
	<10 cig per day	0	1.02	0.55	-	1.88
	10-19 cig per day	0	1.21	0.61	-	2.39
	20+ cig/day	0	2.43	0.75	-	7.90
Ill-defined causes	Never smoker	201	Ref			
	Former smoker	127	1.39	1.05	-	1.82
	<10 cig per day	24	1.21	0.78	-	1.88
	10-19 cig per day	48	2.52	1.75	-	3.62
	20+ cig/day	11	2.48	1.30	-	4.74
External causes	Never smoker	168	1.00	1.00		1.00
	Former smoker	98	1.13	0.85	-	1.50
	<10 cig per day	42	1.86	1.30	-	2.65
	10-19 cig per day	64	2.16	1.57	-	2.99
	20+ cig/day	23	3.26	2.03	-	5.23

[1] Each cause of death is examined in a separate model with age as the time scale, adjusted for alcohol and in strata of sex and education.

Supplementary Table S7: Associations between self-reported smoking status and all-cause and cause-specific mortality – the UK Biobank (2006-10).

Cause[1]	Smoking	Deaths	HR	95 % CI		
All-cause mortality	Never smoker	3434	Ref			
	Former smoker	3938	1.44	1.37	-	1.51
	<10 cigarettes per day	187	2.18	1.88	-	2.53
	10-19 cigarettes per day	557	2.76	2.52	-	3.02
	20+ cigarettes/day	738	3.79	3.49	-	4.11
Infectious diseases	Never smoker	31	Ref			
	Former smoker	26	1.16	0.68	-	1.98
	<10 cigarettes per day	1	1.35	0.18	-	9.93
	10-19 cigarettes per day	8	4.86	2.21	-	10.70
	20+ cigarettes/day	12	8.13	4.07	-	16.27
Neoplasms	Never smoker	2168	Ref			
	Former smoker	2428	1.45	1.36	-	1.54
	<10 cigarettes per day	108	2.00	1.65	-	2.43
	10-19 cigarettes per day	315	2.59	2.30	-	2.92
	20+ cigarettes/day	408	3.62	3.25	-	4.03
Metabolic diseases	Never smoker	33	Ref			
	Former smoker	31	1.18	0.71	-	1.96
	<10 cigarettes per day	0				
	10-19 cigarettes per day	3	1.20	0.36	-	3.96
	20+ cigarettes/day	3	1.11	0.33	-	3.69
Mental disorders	Never smoker	31	Ref			
	Former smoker	29	1.12	0.66	-	1.88
	<10 cigarettes per day	2	3.02	0.72	-	12.69
	10-19 cigarettes per day	1	0.62	0.08	-	4.59
	20+ cigarettes/day	8	5.26	2.37	-	11.69
Nervous system	Never smoker	158	Ref			
	Former smoker	115	0.93	0.73	-	1.19
	<10 cigarettes per day	6	1.58	0.70	-	3.57
	10-19 cigarettes per day	5	0.58	0.24	-	1.41
	20+ cigarettes/day	13	1.60	0.90	-	2.84
Circulatory diseases	Never smoker	648	Ref			
	Former smoker	860	1.55	1.39	-	1.72
	<10 cigarettes per day	46	2.89	2.14	-	3.90
	10-19 cigarettes per day	132	3.22	2.67	-	3.89
	20+ cigarettes/day	163	3.84	3.22	-	4.58
Respiratory diseases	Never smoker	131	Ref			
	Former smoker	239	2.10	1.69	-	2.61
	<10 cigarettes per day	12	3.57	1.98	-	6.46
	10-19 cigarettes per day	50	5.83	4.20	-	8.11
	20+ cigarettes/day	62	7.21	5.28	-	9.84
Digestive system	Never smoker	132	Ref			

	Former smoker	129	1.13	0.88	-	1.45
	<10 cigarettes per day	8	2.14	1.05	-	4.38
	10-19 cigarettes per day	30	3.20	2.14	-	4.78
	20+ cigarettes/day	54	5.30	3.81	-	7.37
Musculoskeltal/	Never smoker	18	Ref			
connective tissue	Former smoker	28	2.38	1.30	-	4.38
	<10 cigarettes per day	1	2.00	0.27	-	15.04
	10-19 cigarettes per day	0				
	20+ cigarettes/day	1	0.90	0.12	-	6.89
Genitourinary	Never smoker	16	Ref			
	Former smoker	20	1.69	0.86	-	3.33
	<10 cigarettes per day	1	2.57	0.34	-	19.52
	10-19 cigarettes per day	2	2.02	0.46	-	8.90
	20+ cigarettes/day	1	1.06	0.14	-	8.11
Ill-defined causes	Never smoker	21	Ref			
	Former smoker	11	0.81	0.39	-	1.70
	<10 cigarettes per day	0				
	10-19 cigarettes per day	6	3.90	1.53	-	9.89
	20+ cigarettes/day	10	5.72	2.58	-	12.70
External causes	Never smoker	21	Ref			
	Former smoker	12	0.77	0.37	-	1.59
	<10 cigarettes per day	0				
	10-19 cigarettes per day	2	1.51	0.35	-	6.50
	20+ cigarettes/day	3	2.36	0.68	-	8.18

[1] Each cause of death is examined in a separate model with age as the time scale, adjusted for alcohol and in strata of sex and education.

Supplementary Table S8: Associations between self-reported smoking status and all-cause and cause-specific mortality –the HUNT2 Study (1995-97). Analyses performed separately up to age 70, from age 70-85 and aged 85 onwards. N=52,561.

		Before 70 years old					70-85 years old					85+ years old				
Cause[1]		Deaths	HR	95% CI			Deaths	HR	95% CI			Deaths	HR	95% CI		
All-cause mortality[2]	Never smoker	445	Ref				1482	Ref				2306	Ref			
	Former smoker	462	1.34	1.17	-	1.53	1634	1.38	1.28	-	1.50	1085	1.15	1.05	-	1.26
	<10 cig per day	223	2.01	1.70	-	2.37	559	1.88	1.70	-	2.07	243	1.44	1.26	-	1.65
	10-19 cig per day	455	2.21	1.93	-	2.53	608	2.42	2.19	-	2.68	133	1.52	1.27	-	1.83
	20+ cig/day	188	3.45	2.89	-	4.12	124	3.11	2.57	-	3.76	18	1.55	0.97	-	2.47
Infectious diseases	Never smoker	3	Ref				32	Ref				66	Ref			
	Former smoker	2	0.79	0.13	-	5.00	31	1.52	0.86	-	2.68	31	1.27	0.74	-	2.17
	<10 cig per day	1	1.36	0.14	-	13.44	3	0.56	0.17	-	1.86	7	1.67	0.74	-	3.76
	10-19 cig per day	6	4.42	1.04	-	18.78	12	2.99	1.47	-	6.07	2	0.85	0.20	-	3.62
	20+ cigarettes/day	1	2.88	0.28	-	29.60	1	1.92	0.25	-	14.42	2	7.04	1.65	-	30.09
Neoplasms	Never smoker	208	Ref				423	Ref				305	Ref			
	Former smoker	225	1.45	1.19	-	1.76	496	1.35	1.16	-	1.56	223	1.35	1.10	-	1.67
	<10 cig per day	104	1.94	1.52	-	2.46	178	1.91	1.59	-	2.29	38	1.30	0.92	-	1.85
	10-19 cig per day	225	2.39	1.97	-	2.91	212	2.54	2.13	-	3.03	34	2.24	1.54	-	3.25
	20+ cig/day	80	3.57	2.73	-	4.67	45	3.25	2.36	-	4.47	0				
Metabolic diseases	Never smoker	14	Ref				51	Ref				59	Ref			
	Former smoker	12	1.08	0.48	-	2.41	31	0.84	0.51	-	1.40	22	0.82	0.45	-	1.49
	<10 cig per day	2	0.64	0.14	-	2.88	10	1.02	0.51	-	2.05	5	1.13	0.43	-	2.91
	10-19 cig per day	6	0.91	0.34	-	2.43	10	1.24	0.61	-	2.52	1	0.46	0.06	-	3.43
	20+ cig/day	2	1.02	0.23	-	4.60	3	2.58	0.78	-	8.59	0				

Mental disorders[2]	Never smoker	4	Ref				41	Ref				112	Ref			
	Former smoker	1	0.34	0.04	-	3.11	36	1.47	0.87	-	2.49	43	1.27	0.82	-	1.96
	<10 cig per day	2	2.25	0.40	-	12.56	7	1.09	0.48	-	2.48	11	1.56	0.82	-	2.97
	10-19 cig per day	9	5.12	1.50	-	17.51	8	1.78	0.80	-	3.92	2	0.57	0.14	-	2.37
	20+ cig/day	5	7.96	1.94	-	32.70	1	1.89	0.25	-	14.08	0				
Nervous system[2]	Never smoker	23	Ref				54	Ref				64	Ref			
	Former smoker	13	0.86	0.42	-	1.74	45	1.07	0.68	-	1.68	36	1.58	0.94	-	2.64
	<10 cig per day	11	2.31	1.10	-	4.84	16	1.44	0.81	-	2.57	2	0.41	0.10	-	1.70
	10-19 cig per day	11	1.13	0.54	-	2.39	12	1.27	0.66	-	2.45	3	1.22	0.37	-	4.02
	20+ cig/day	5	1.80	0.67	-	4.87	2	1.27	0.30	-	5.36	0				
Circulatory diseases[2]	Never smoker	106	Ref				628	Ref				1140	Ref			
	Former smoker	127	1.33	1.02	-	1.73	701	1.38	1.22	-	1.56	470	1.02	0.90	-	1.17
	<10 cig per day	64	2.43	1.77	-	3.33	228	1.82	1.56	-	2.14	110	1.34	1.10	-	1.65
	10-19 cig per day	101	1.98	1.50	-	2.63	218	2.09	1.78	-	2.46	44	1.02	0.75	-	1.39
	20+ cig/day	48	3.21	2.25	-	4.57	43	2.65	1.92	-	3.64	8	1.45	0.72	-	2.92
Respiratory diseases[2]	Never smoker	10	Ref				82	Ref				164	Ref			
	Former smoker	17	2.38	1.07	-	5.31	129	2.00	1.47	-	2.72	94	1.38	1.01	-	1.89
	<10 cig per day	11	4.22	1.77	-	10.09	67	4.20	2.99	-	5.88	32	2.81	1.88	-	4.21
	10-19 cig per day	14	3.27	1.42	-	7.52	71	5.70	4.05	-	8.01	21	3.58	2.20	-	5.82
	20+ cig/day	18	17.00	7.43	-	38.88	19	9.84	5.81	-	16.67	3	3.84	1.20	-	12.27
Digestive system	Never smoker	6	Ref				41	Ref				57	Ref			
	Former smoker	8	1.70	0.58	-	5.04	29	1.10	0.64	-	1.87	30	1.56	0.91	-	2.68
	<10 cig per day	2	1.12	0.22	-	5.65	15	1.97	1.07	-	3.65	12	3.18	1.65	-	6.14
	10-19 cig per day	14	4.36	1.62	-	11.73	23	3.77	2.16	-	6.56	6	3.25	1.34	-	7.91
	20+ cig/day	5	6.88	2.00	-	23.63										

Musculo-skeltal/ connective tissue	Never smoker	3	Ref				13	Ref				14	Ref			
	Former smoker	2	0.69	0.11	-	4.35	8	0.73	0.28	-	1.95	5	0.71	0.21	-	2.40
	<10 cig per day	1	0.93	0.09	-	9.22	3	0.93	0.26	-	3.37	1	0.73	0.09	-	5.84
	10-19 cig per day	2	1.02	0.16	-	6.37	4	1.45	0.45	-	4.70	1	1.56	0.19	-	12.72
	20+ cig/day						1	2.68	0.33	-	21.80					
Genitourinary	Never smoker	4	Ref				35	Ref				72	Ref			
	Former smoker	0	0.00	0.00	-	0.00	42	1.78	1.05	-	3.01	33	1.15	0.69	-	1.91
	<10 cig per day	1	1.36	0.14	-	12.97	4	0.69	0.24	-	1.99	7	1.35	0.60	-	3.02
	10-19 cig per day						8	1.79	0.80	-	4.03	2	0.81	0.19	-	3.36
	20+ cig/day	1	4.94	0.52	-	46.49						2	5.78	1.35	-	24.78
Ill-defined causes	Never smoker	13	Ref				38	Ref				150	Ref			
	Former smoker	20	1.49	0.73	-	3.04	43	1.51	0.92	-	2.47	64	1.33	0.91	-	1.93
	<10 cig per day	3	0.85	0.24	-	3.02	13	1.80	0.94	-	3.45	8	0.94	0.45	-	1.95
	10-19 cig per day	21	2.69	1.32	-	5.48	20	3.25	1.81	-	5.83	7	1.72	0.78	-	3.78
	20+ cig/day	5	1.85	0.64	-	5.36	6	5.21	2.07	-	13.11					
External causes	Never smoker	42	Ref				41	Ref				85	Ref			
	Former smoker	34	1.32	0.82	-	2.11	35	1.27	0.76	-	2.12	29	0.86	0.52	-	1.42
	<10 cig per day	20	2.15	1.25	-	3.72	13	1.83	0.96	-	3.50	9	1.58	0.77	-	3.22
	10-19 cig per day	46	2.40	1.55	-	3.72	8	1.38	0.63	-	3.05	10	3.16	1.56	-	6.41
	20+ cig/day	18	3.32	1.86	-	5.92	3	3.23	0.95	-	10.95	2	4.95	1.18	-	20.77

[1] Each cause of death is examined in a separate model with age as the time scale, adjusted for alcohol and in strata of sex and education.

[2] Non-proportionality indicated by Schoenfeld's residuals when analysing all ages combined

Abbreviations: cig=cigarettes

Supplementary Table S9: Associations between self-reported smoking status and all-cause and cause-specific mortality –the UK Biobank (2006-10). Analyses performed separately up to age 70 and aged 70 onwards.

		Before 70 years old					From 70 years old*				
		Deaths	HR	95% CI			Deaths	HR	95% CI		
All-cause mortality	Never smoker	3556	1	Ref			1047	1	Ref		
	Former smoker	4051	1.44	1.36	-	1.52	1443	1.42	1.31	-	1.54
	<10 cig per day	201	2.30	1.95	-	2.72	54	2.39	1.82	-	3.13
	10-19 cig per day	582	4.61	4.23	-	5.03	134	3.27	2.73	-	3.92
	20+ cig/day	778	3.09	2.80	-	3.42	134	2.73	2.28	-	3.27
Infectious diseases	Never smoker	32	1	Ref			7	1	Ref		
	Former smoker	26	1.15	0.64	-	2.08	6	0.89	0.30	-	2.69
	<10 cig per day	1					1	6.44	0.79	-	52.32
	10-19 cig per day	9	7.67	3.66	-	16.09	1	11.00	2.81	-	43.14
	20+ cig/day	13	5.74	2.59	-	12.74	3	3.02	0.37	-	24.60
Neoplasms	Never smoker	2173	1	Ref			637	1	Ref		
	Former smoker	2427	1.48	1.38	-	1.59	817	1.35	1.22	-	1.50
	<10 cig per day	110	2.02	1.61	-	2.53	30	2.14	1.48	-	3.08
	10-19 cig per day	319	4.06	3.60	-	4.58	71	3.42	2.72	-	4.31
	20+ cig/day	413	2.84	2.49	-	3.25	83	2.40	1.88	-	3.07
Metabolic diseases	Never smoker	33	1	Ref			5	1	Ref		
	Former smoker	31	0.85	0.45	-	1.58	15	2.73	0.99	-	7.59
	<10 cig per day	0	0.00	0.00	-		0				
	10-19 cig per day	3	1.17	0.28	-	4.93	0	4.40	0.51	-	37.86
	20+ cig/day	3	1.77	0.54	-	5.83	1				
Mental disorders	Never smoker	32	1	Ref			20	1	Ref		
	Former smoker	30	1.13	0.50	-	2.56	19	0.93	0.49	-	1.76
	<10 cig per day	2					2	4.66	1.09	-	19.95
	10-19 cig per day	1	7.69	2.90	-	20.37	0	2.46	0.57	-	10.59

	20+ cig/day	8	1.30		0.17	-	9.98	2				
Nervous system	Never smoker	156	1	Ref				56	1	Ref		
	Former smoker	116	0.83		0.61	-	1.14	53	1.00		0.68	- 1.46
	<10 cig per day	6	1.85		0.75	-	4.54	1	0.82		0.11	- 5.90
	10-19 cig per day	5	1.62		0.82	-	3.21	1	2.36		0.94	- 5.91
	20+ cig/day	14	0.67		0.25	-	1.82	5	0.39		0.05	- 2.80
Circulatory disease	Never smoker	659	1	Ref				187	1	Ref		
	Former smoker	862	1.46		1.29	-	1.65	328	1.72		1.43	- 2.06
	<10 cig per day	46	3.05		2.17	-	4.30	12	2.92		1.63	- 5.23
	10-19 cig per day	131	5.04		4.18	-	6.08	35	3.21		2.11	- 4.88
	20+ cig/day	169	3.51		2.82	-	4.37	25	3.87		2.70	- 5.56
Respiratory disease	Never smoker	129	1	Ref				66	1	Ref		
	Former smoker	240	2.59		1.93	-	3.47	108	1.66		1.21	- 2.26
	<10 cig per day	12	4.85		2.33	-	10.09	4	3.48		1.40	- 8.64
	10-19 cig per day	51	13.48		9.35	-	19.44	17	4.96		2.73	- 9.01
	20+ cig/day	64	8.87		5.88	-	13.40	13	5.50		3.22	- 9.38
Digestive system	Never smoker	133	1	Ref				34	1	Ref		
	Former smoker	132	1.24		0.93	-	1.65	41	1.23		0.77	- 1.95
	<10 cig per day	9	2.83		1.32	-	6.09	2	2.67		0.64	- 11.13
	10-19 cig per day	31	8.76		6.26	-	12.25	6	1.48		0.35	- 6.16
	20+ cig/day	55	4.26		2.75	-	6.61	2	3.73		1.56	- 8.88
Musculo-skeltal/ connective tissue	Never smoker	17	1	Ref				3	1	Ref		
	Former smoker	29	1.76		0.87	-	3.57	12	4.81		1.34	- 17.26
	<10 cig per day	1	2.34		0.31	-	17.73	0				
	10-19 cig per day	0	1.20		0.16	-	9.13	0				
	20+ cig/day	1						0				
Genitourinary	Never smoker	16	1	Ref				5	1	Ref		
	Former smoker	20	1.00		0.40	-	2.52	12	2.65		0.92	- 7.65
	<10 cig per day	1						1	9.25		1.08	- 79.22
	10-19 cig per day	2	1.70		0.22	-	13.26	0				
	20+ cig/day	1	3.21		0.71	-	14.48	0				

Ill-defined causes	Never smoker	21	1	Ref			3	1	Ref			
	Former smoker	11	0.73	0.31	-	1.68	3	0.98	0.19	-	4.98	
	<10 cig per day	0					0					
	10-19 cig per day	6	8.32	3.82	-	18.12	0					
	20+ cig/day	10	5.25	2.08	-	13.24	0					
External causes	Never smoker	21	1	Ref			2	1	Ref			
	Former smoker	12	0.89	0.42	-	1.88	1	0.49	0.04	-	5.50	
	<10 cig per day	0					0					
	10-19 cig per day	2	3.73	1.26	-	11.02	0					
	20+ cig/day	4	1.75	0.41	-	7.50	0					

Abbreviations: cig=cigarettes

***** There were no deaths after age 80 in the UK Biobank study sample

Supplementary Table S10: Hazard ratios for all-cause and cause specific mortality per effect allele of rs1051730 in never smokers (N=24,747), and ever smokers (N=31,272). The HUNT2 Study (1995-97).

	Never smokers				Ever smokers				
	Deaths	HR	95% CI		Deaths	HR	95% CI		P[1]
All-cause	4709	1.02	0.98 - 1.06		6594	1.12	1.08 - 1.16		<0.001
Infectious diseases	108	1.02	0.77 - 1.35		113	1.13	0.86 - 1.49		0.576
Neoplasms	1029	0.98	0.89 - 1.07		2109	1.19	1.12 - 1.27		<0.001
Endocrine diseases	138	1.22	0.96 - 1.55		120	1.30	1.00 - 1.69		0.709
Mental disorders	174	0.96	0.77 - 1.20		145	0.91	0.71 - 1.18		0.777
Neurological disorders	160	0.91	0.72 - 1.15		179	1.00	0.80 - 1.25		0.552
Cardiovascular diseases	2101	1.06	0.99 - 1.12		2502	1.08	1.01 - 1.14		0.532
Respiratory diseases	285	0.97	0.82 - 1.16		581	1.26	1.12 - 1.42		0.011
Diseases of digestive system	117	1.05	0.80 - 1.37		167	1.05	0.84 - 1.32		0.979
Musculoskeletal / connective tissue diseases									
Diseases of genitourinary system	121	0.93	0.71 - 1.21		119	0.96	0.73 - 1.26		0.852
Unknown cause	222	1.09	0.90 - 1.32		236	1.06	0.87 - 1.28		0.814
External causes	188	1.02	0.82 - 1.26		269	1.10	0.92 - 1.32		0.515

[1] P for different association between rs1051730 and mortality depending on smoking status.

Supplementary Table S11: Hazard ratios for all-cause and cause specific mortality per effect allele of rs1051730 in never smokers (N= 248,438), and ever smokers (N= 212,565) in the UK Biobank (2006-10)

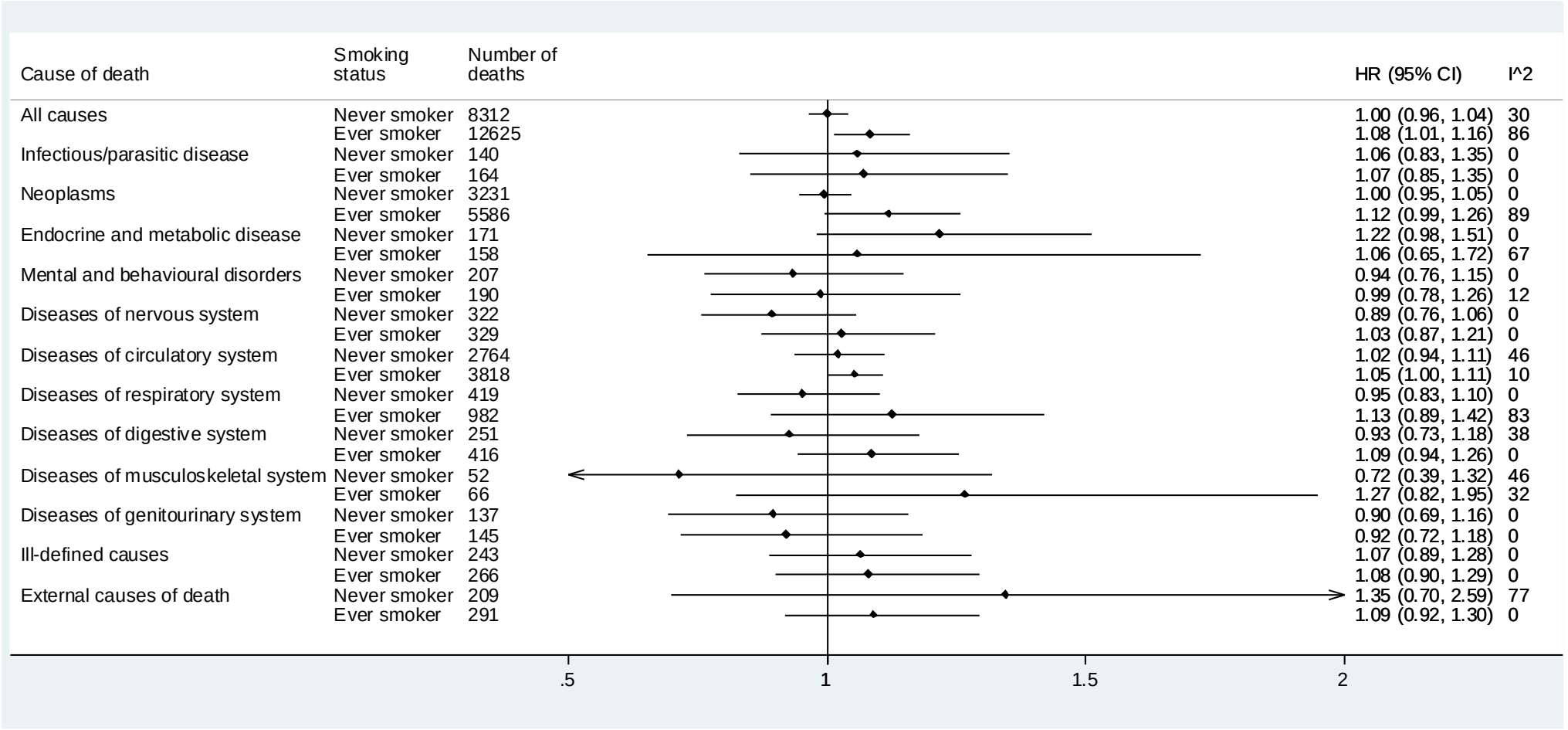
	Never smokers			Ever smokers		
	Deaths	HR	95% CI	Deaths	HR	95% CI
All-cause mortality	3603	0.98	0.93 - 1.03	6031	1.05	1.01 - 1.09
Infectious diseases	32	1.20	0.72 - 1.99	51	0.94	0.62 - 1.43
Neoplasms	2202	1.00	0.94 - 1.07	3477	1.06	1.00 - 1.11
Endocrine diseases	33	1.22	0.74 - 2.01	38	0.79	0.47 - 1.30
Mental disorders	33	0.81	0.47 - 1.38	45	1.20	0.78 - 1.84
Neurological disorders	162	0.88	0.70 - 1.12	150	1.06	0.84 - 1.35
Cardiovascular diseases	663	0.96	0.86 - 1.08	1316	1.02	0.94 - 1.11
Respiratory diseases	134	0.91	0.71 - 1.18	401	1.00	0.86 - 1.15
Diseases of digestive system	134	0.82	0.63 - 1.07	249	1.11	0.93 - 1.34
Musculoskeletal / connective tissue diseases	18	1.01	0.50 - 2.01	35	1.55	0.97 - 2.49
Diseases of genitourinary system	16	0.66	0.30 - 1.48	26	0.76	0.41 - 1.41
Unknown cause	21	0.81	0.41 - 1.57	30	1.27	0.75 - 2.14
External causes	21	2.01	1.10 - 3.68	22	0.95	0.51 - 1.80

Supplementary Table S12: Hazard ratios for all-cause and cause specific mortality per effect allele of rs1051730 in ever smokers (N=31,272), analysed separately before and after the age of 80. The HUNT2 Study (1995-97).

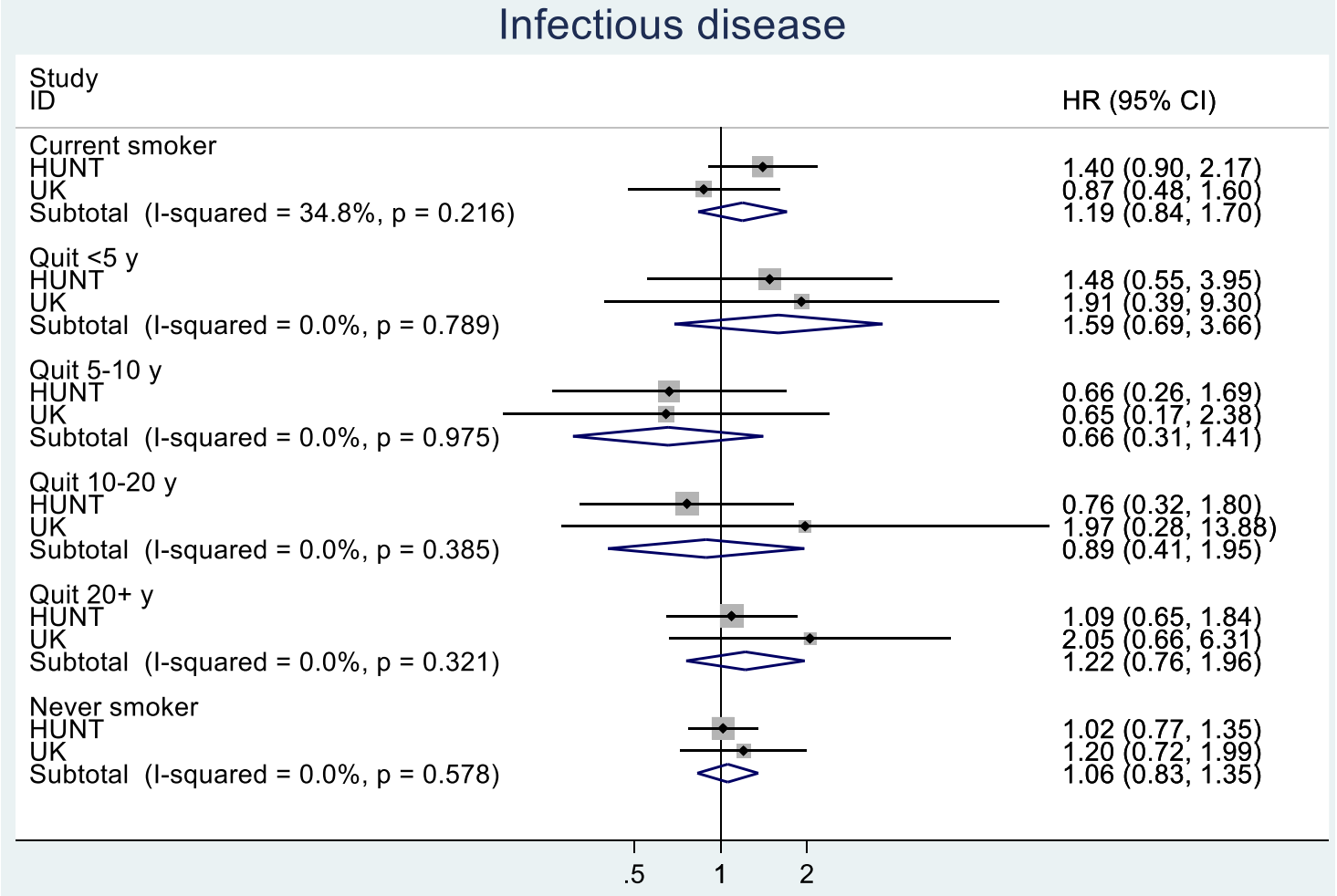
	Death before age 80					Death after age 80					
	Deaths	HR	95% CI			Deaths	HR	95% CI			p interaction[1]
All-cause	3446	1.15	1.09	-	1.21	3148	1.09	1.04	-	1.15	0.197
Infectious diseases	40	1.35	0.86	-	2.11	73	1.02	0.72	-	1.46	0.343
Neoplasms	1383	1.19	1.10	-	1.29	726	1.19	1.07	-	1.33	0.984
Endocrine diseases	59	1.58	1.10	-	2.28	61	1.06	0.72	-	1.55	0.136
Mental disorders	38	0.92	0.57	-	1.49	107	0.91	0.68	-	1.23	0.978
Neurological disorders	96	1.07	0.80	-	1.44	83	0.91	0.65	-	1.28	0.485
Cardiovascular diseases	1172	1.05	0.97	-	1.15	1330	1.10	1.01	-	1.19	0.505
Respiratory diseases	239	1.48	1.24	-	1.78	342	1.12	0.96	-	1.31	0.024
Diseases of digestive system	82	1.06	0.77	-	1.47	85	1.04	0.75	-	1.44	0.922
Diseases of genitourinary system	32	1.08	0.64	-	1.81	87	0.91	0.66	-	1.27	0.601
Unknown cause	106	1.27	0.96	-	1.67	130	0.90	0.68	-	1.18	0.081
External causes	176	1.03	0.83	-	1.29	93	1.25	0.93	-	1.69	0.313

[1] P for different association between rs1051730 and mortality depending on age category.

Supplementary Figure S2: Associations between number of smoking increasing alleles of rs1071530 and mortality, results from a random effect meta-analysis of estimates from the HUNT2 Study (1995-1997) and the UK Biobank (2006-2010)

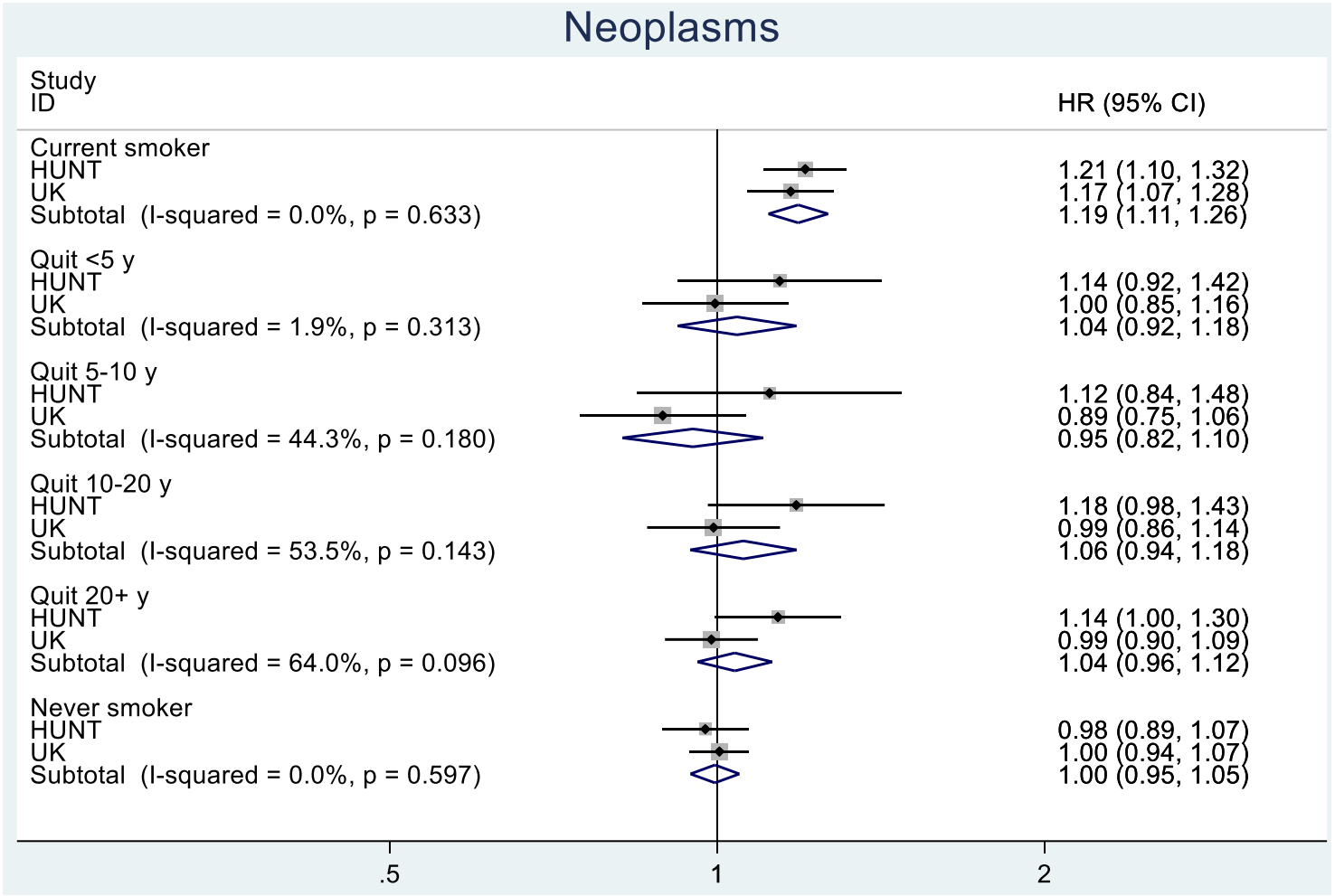


Supplementary Figure S3: Hazard ratios for mortality from infectious and parasitic diseases per effect allele of rs1051730 according to smoking status. Meta-analysis of the HUNT2 Study (1995-97) and the UK Biobank (2006-2010).



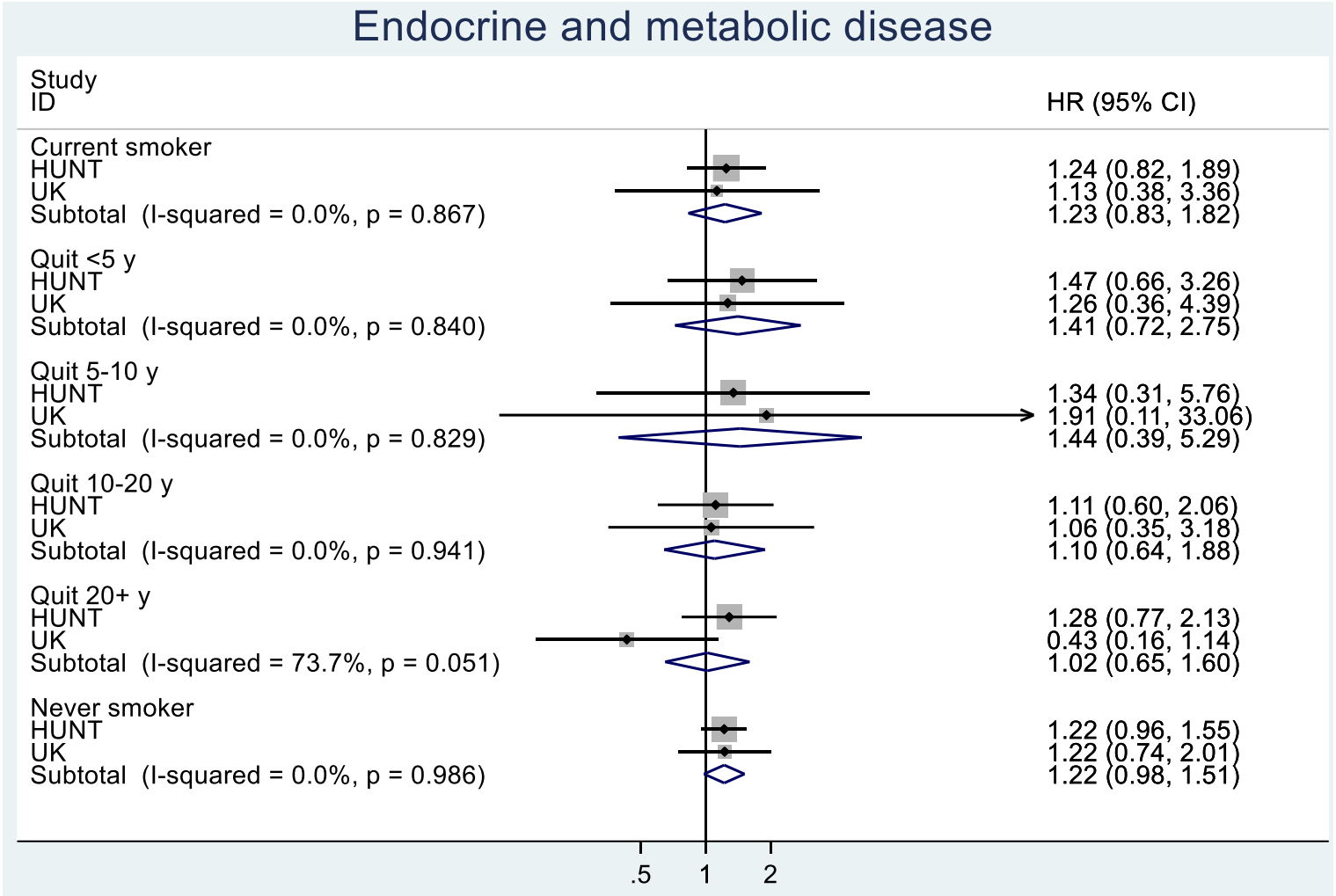
Abbreviations: y=years

Supplementary Figure S4: Hazard ratios for mortality from neoplasms per effect allele of rs1051730 according to smoking status. Meta-analysis of the HUNT2 Study (1995-97) and the UK Biobank (2006-2010).



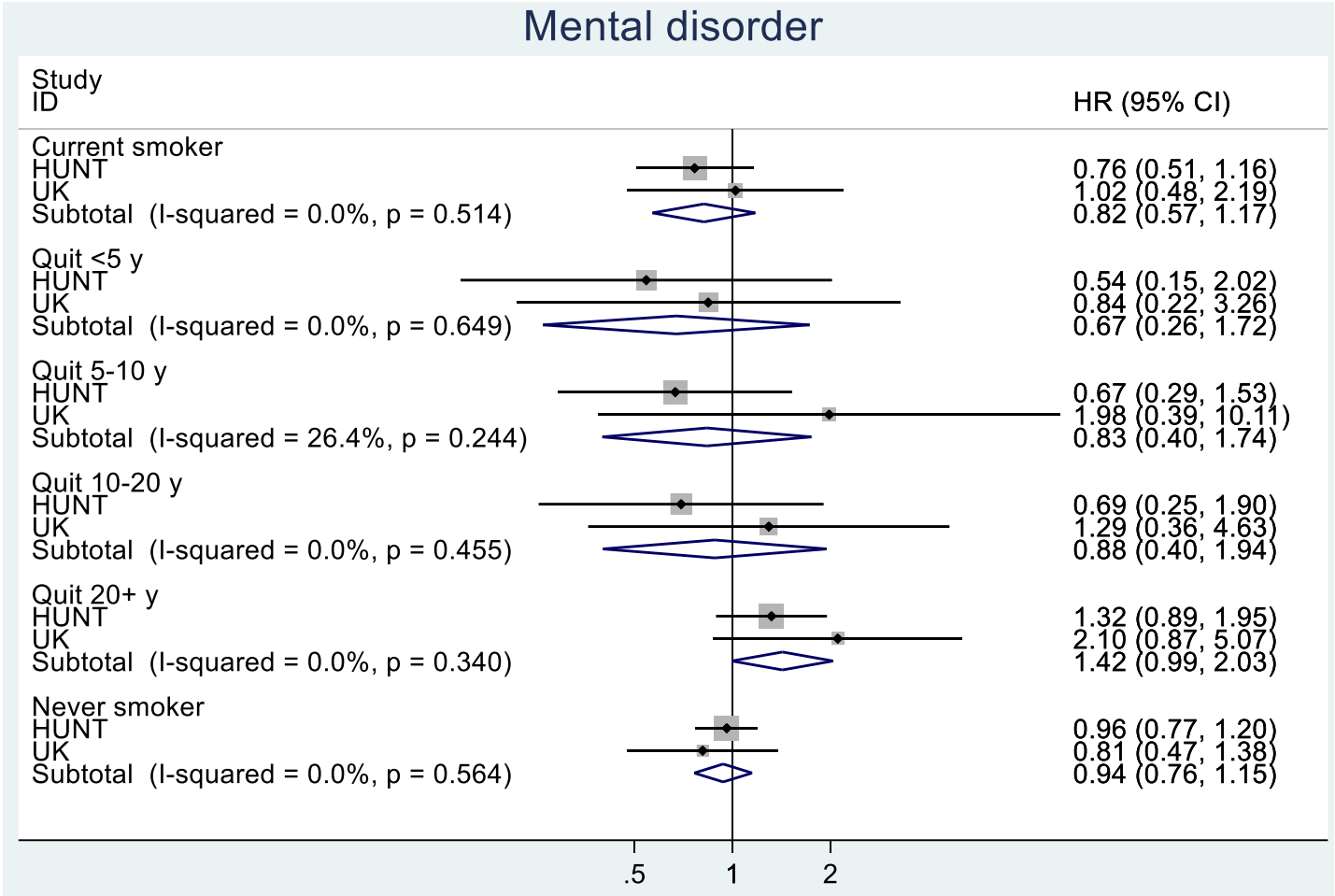
Abbreviations: y=years

Supplementary Figure S5: Hazard ratios for mortality from endocrine and metabolic diseases per effect allele of rs1051730 according to smoking status. Meta-analysis of the HUNT2 Study (1995-97), and the UK Biobank (2006-2010).



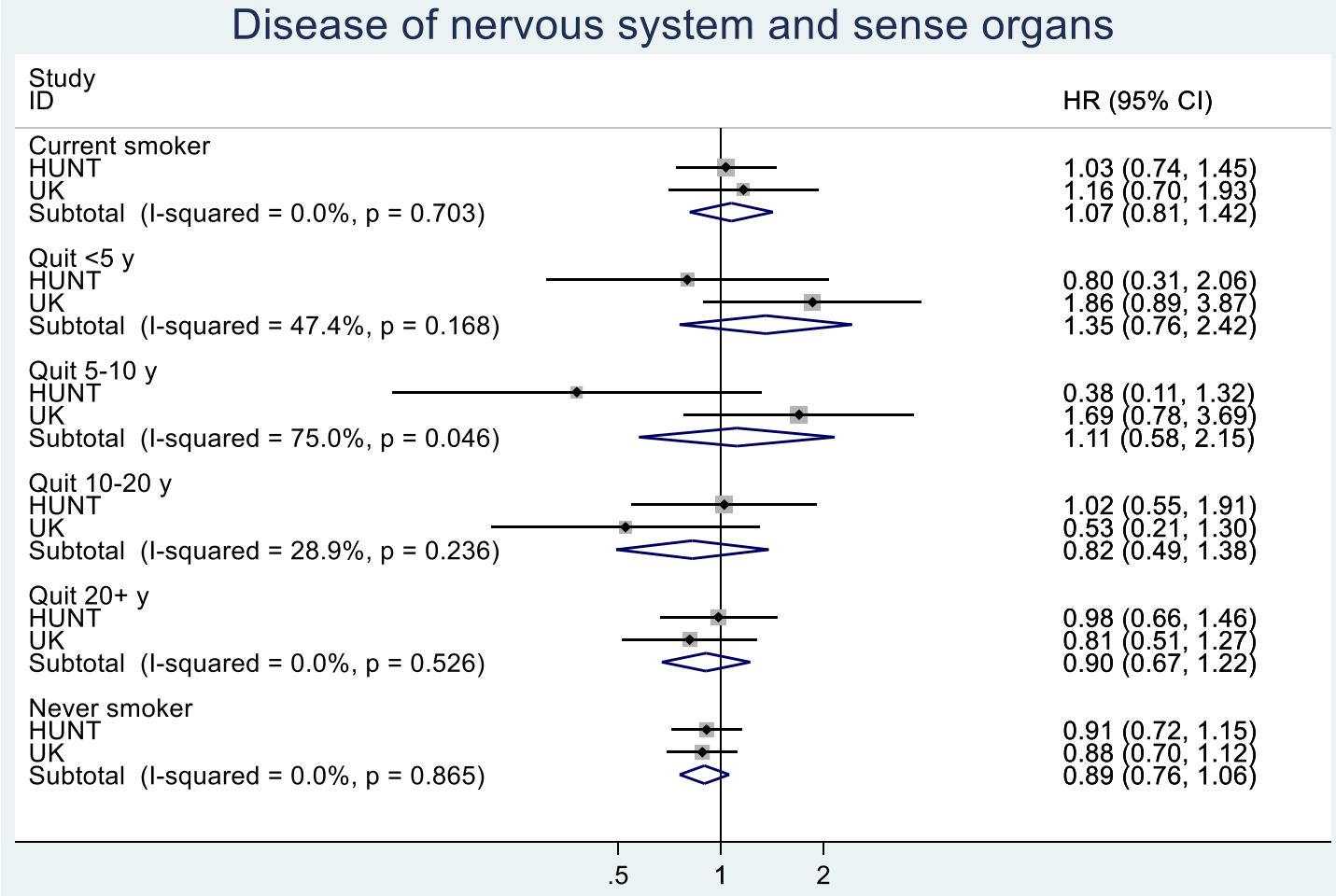
Abbreviations: y=years

Supplementary Figure S6: Hazard ratios for mortality from mental and behavioural disorders per effect allele of rs1051730 according to smoking status. Meta-analysis of the HUNT2 Study (1995-97) and the UK Biobank (2006-2010).



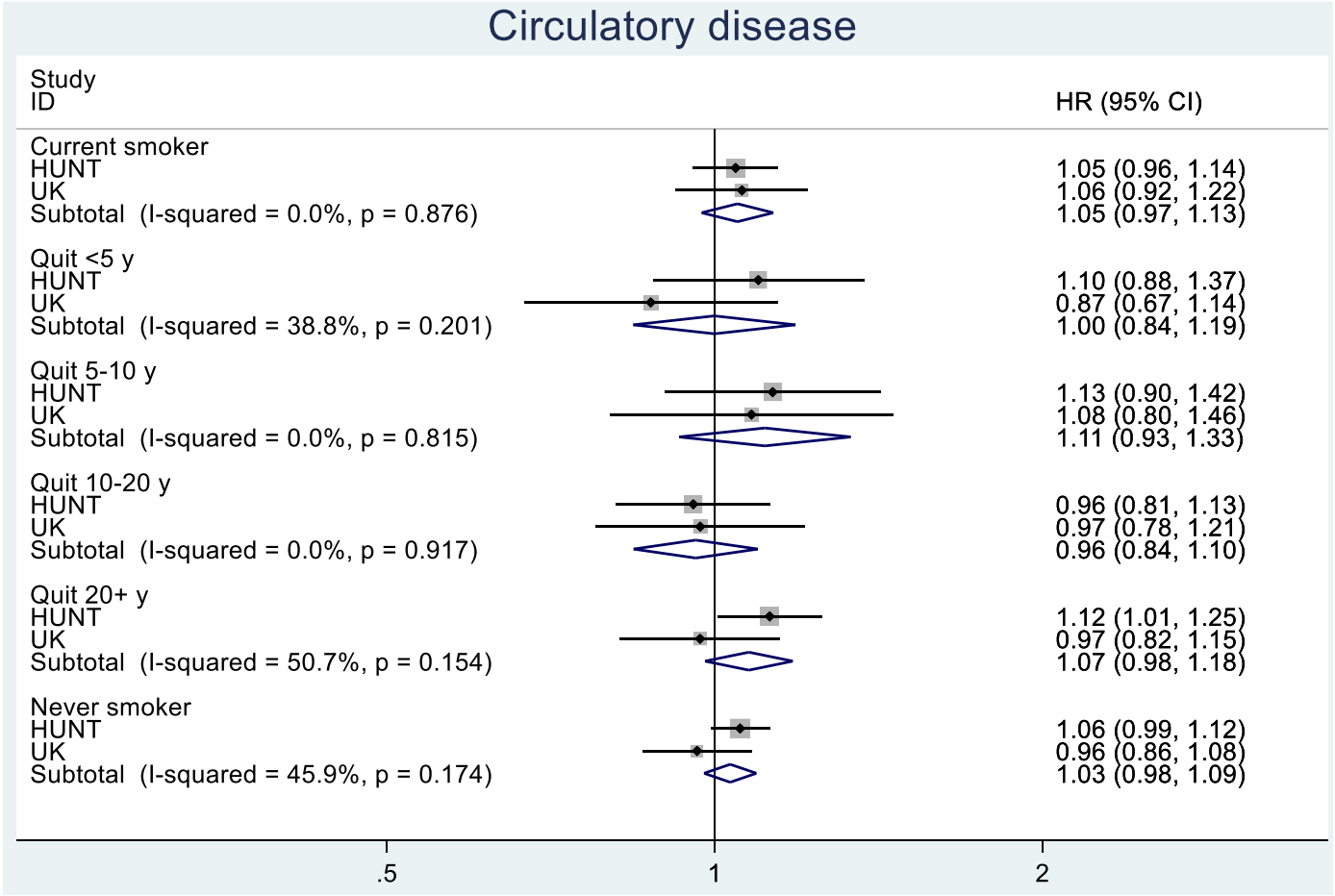
Abbreviations: y=years

Supplementary Figure S7: Hazard ratios mortality from diseases of the nervous system and sense organs per effect allele of rs1051730 according to smoking status. Meta-analysis of the HUNT2 Study (1995-97) and the UK Biobank (2006-2010).



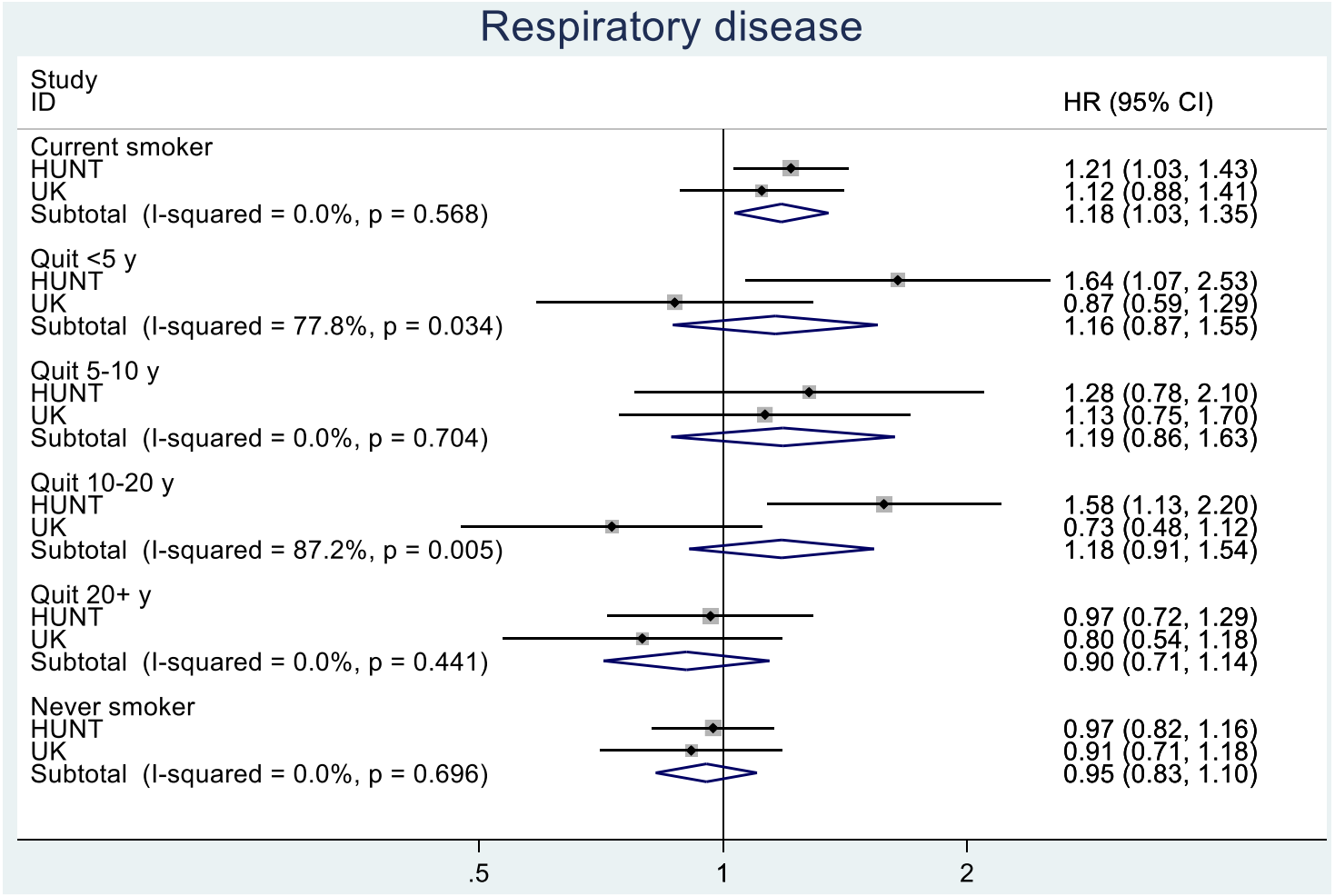
Abbreviations: y=years

Supplementary Figure S8: Hazard ratios for mortality from circulatory diseases per effect allele of rs1051730 according to smoking status. Meta-analysis of the HUNT2 Study (1995-97) and the UK Biobank (2006-2010).



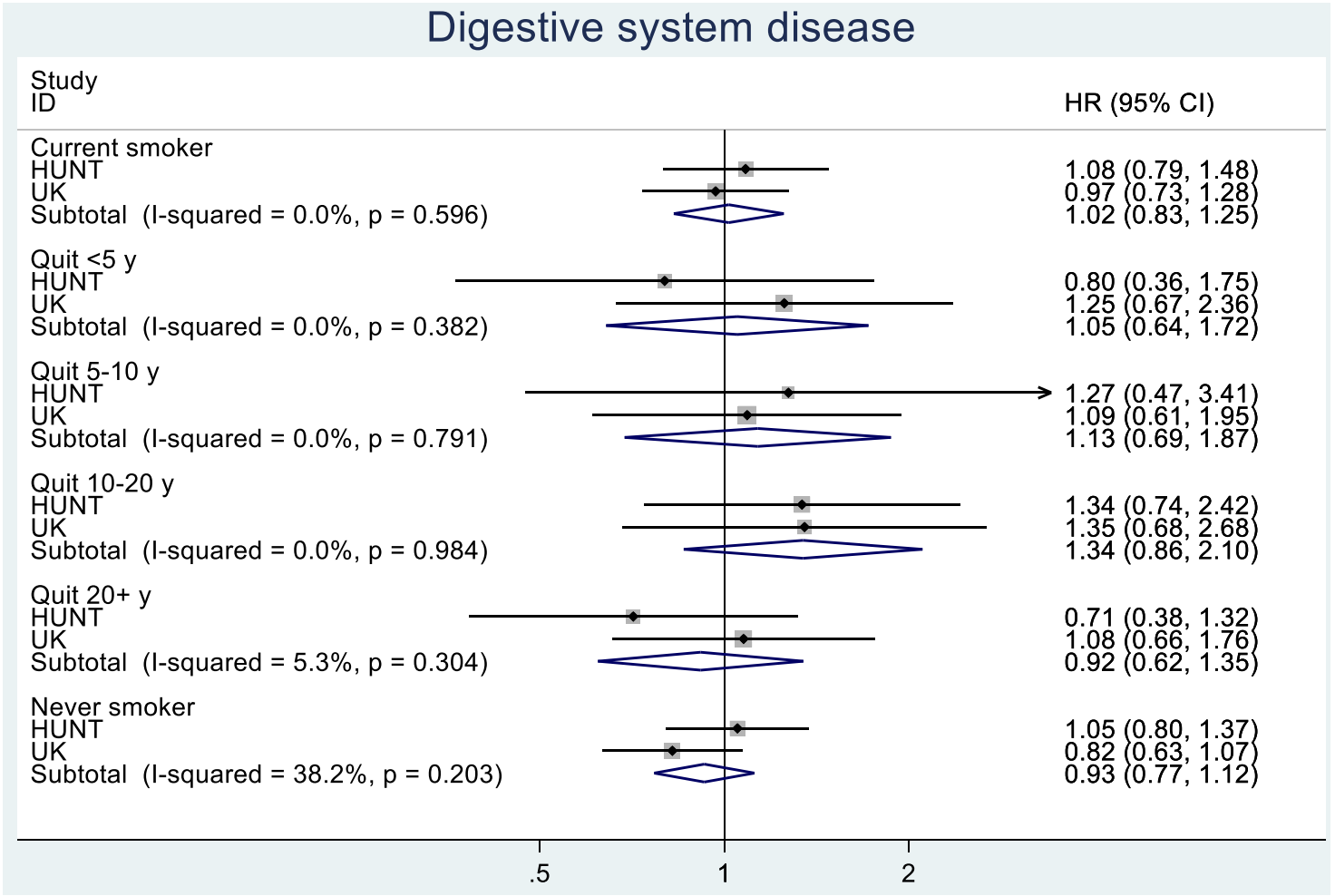
Abbreviations: y=years

Supplementary Figure S9: Hazard ratios for mortality from respiratory diseases per effect allele of rs1051730 according to smoking status. Meta-analysis of HUNT2 Study (1995-97) and the UK Biobank (2006-2010).



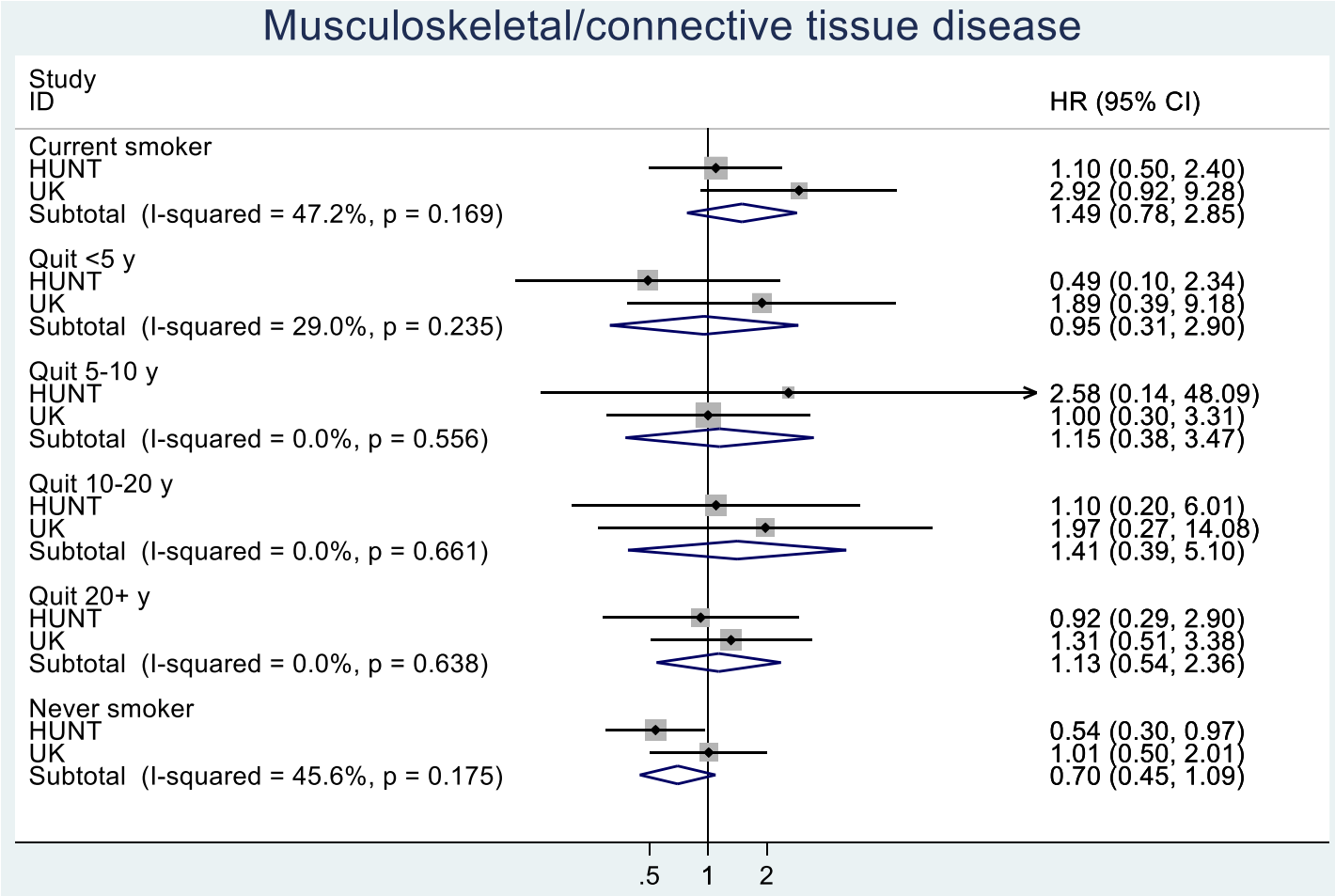
Abbreviations: y=years

Supplementary Figure S10: Hazard ratios for mortality from diseases of the digestive system per effect allele of rs1051730 according to smoking status. Meta-analysis of the HUNT2 Study (1995-97) and the UK Biobank (2006-2010).



Abbreviations: y=years

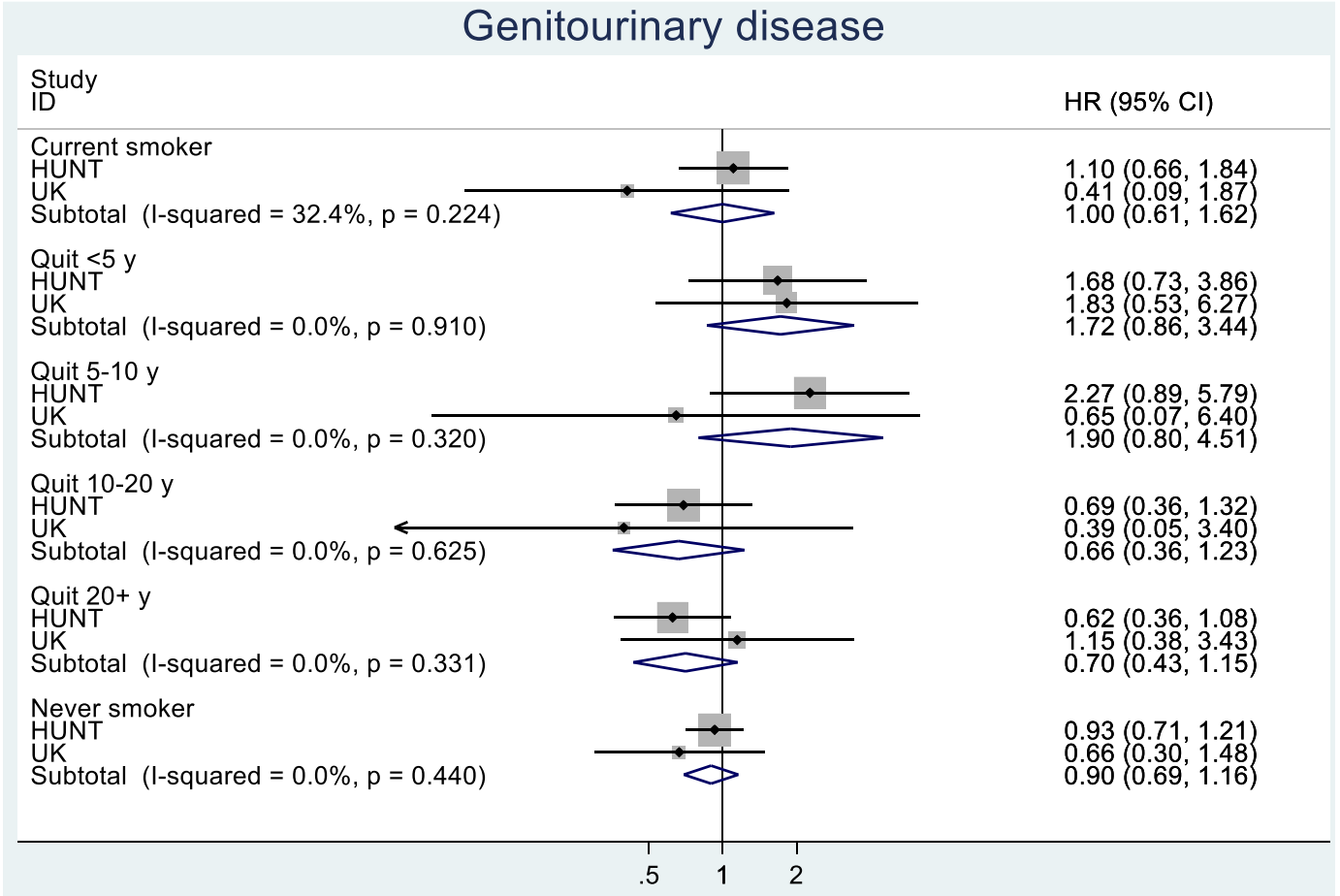
Supplementary Figure S11: Hazard ratios for mortality from diseases of the musculoskeletal system and connective tissue per effect allele of rs1051730 according to smoking status. Meta-analysis of the HUNT2 Study (1995-97) and the UK Biobank (2006-2010).



Abbreviations: y=years

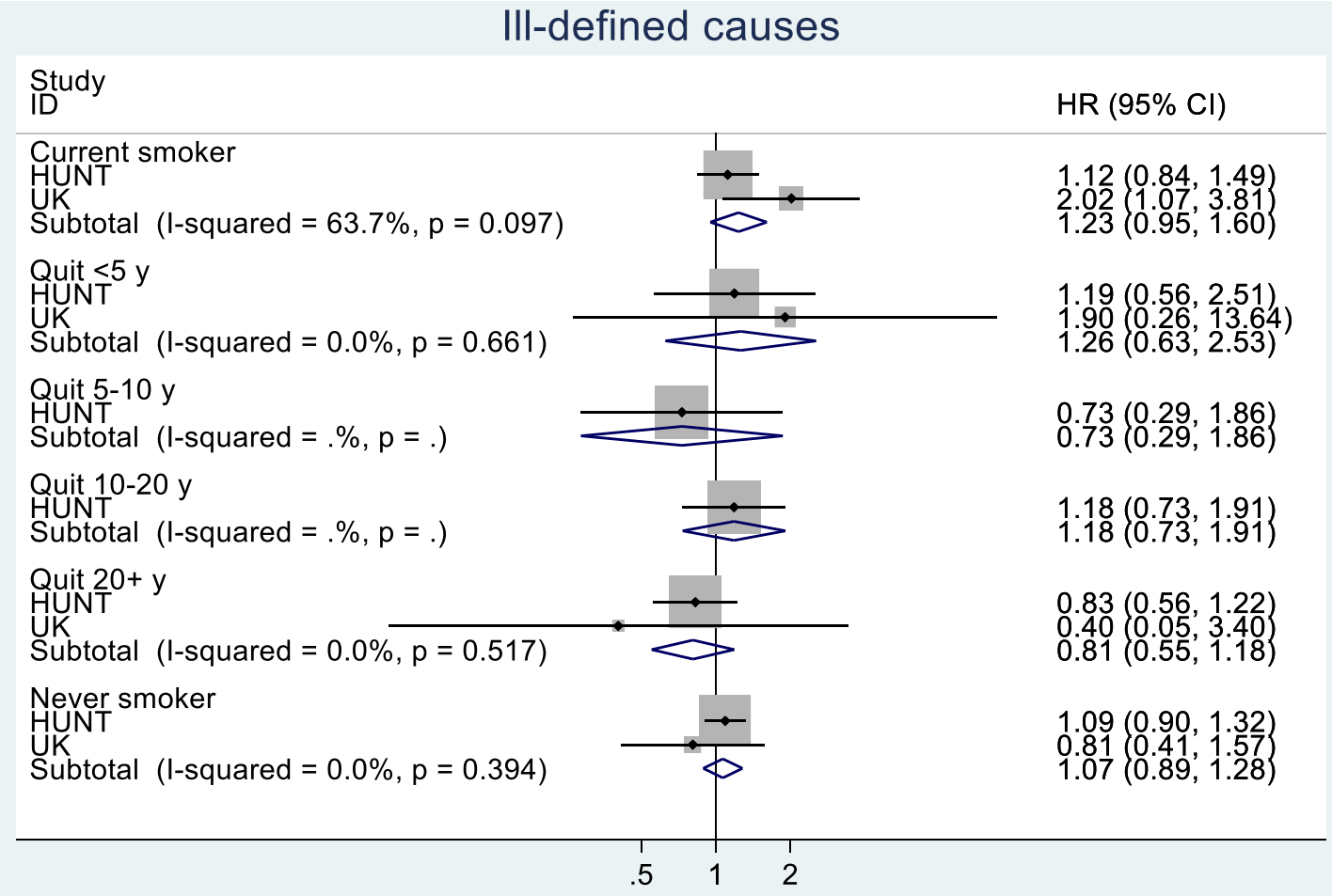
Supplementary Figure S12: Hazard ratios for mortality from genitourinary diseases per effect allele of rs1051730 according to smoking status.

Meta-analysis of the HUNT2 Study (1995-97) and the UK Biobank (2006-2010).



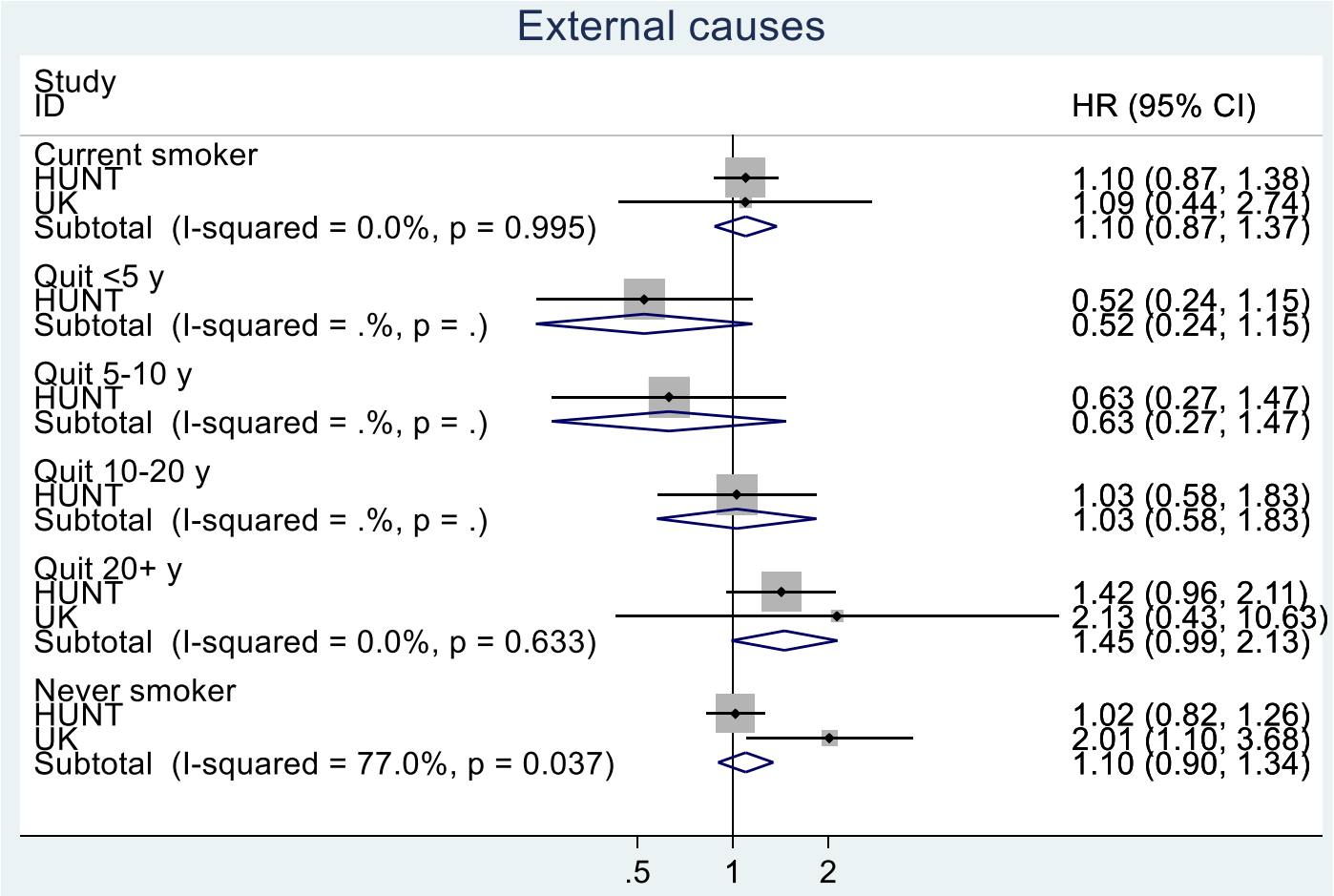
Abbreviations: y=years

Supplementary Figure S13: Hazard ratios for mortality from ill-defined causes per effect allele of rs1051730 according to smoking status. Meta-analysis of the HUNT2 Study (1995-97) and the UK Biobank (2006-2010).



Abbreviations: y=years

Supplementary Figure S14: Hazard ratios for mortality external causes per effect allele of rs1051730 according to smoking status. Meta-analysis of the HUNT2 Study (1995-97) and the UK Biobank (2006-2010).



Abbreviations: y=years

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